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PHYSIOLOGY AND ANATOMY OF THE RESPIRATORY SYSTEM IN THE FETUS AND NEWBORN INFANT

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THE physiology of respiration in the fetus has been poorly understood, and its study has been neglected until recent years. The importance of this subject will be realized when one considers that asphyxia is one of the major causes of death in late prenatal life as well as in the neonatal period.

The placenta is the organ for respiration in the fetus. Its maternal portions develop somewhat in advance of parts contributed by the fetal structures, with the result that the maternal vascular bed in the placenta reaches a large size, while that of the fetal chorion is almost negligible. The maternal blood flowing through the placenta in early fetal life gives up little oxygen to the fetus, whose metabolic needs are small. As fetal growth proceeds, more and more oxygen is taken up in the placenta, and the maternal veins leaving it become darker and darker, containing very little oxygen indeed at the end of gestation. This is illustrated by experiments designed to prevent pregnancy in one uterine horn of the rabbit. The oxygen content of uterine vein blood remained constant throughout pregnancy on the nonpregnant side but declined progressively on the pregnant side.[1, 2]

What are the mechanisms by which the fetus obtains its oxygen in the placenta and what measures of safety are provided against the possibility of asphyxia in utero?

One can picture the placental circulation rather simply. A stream of well-oxygenated maternal blood enters the placenta and comes into intimate contact with the fetal blood stream, poor in oxygen. The two do not mix, but the degree of contact differs in various species of mammals. One might expect the two streams to come into equilibrium in respect to the tensions of their blood gases, the umbilical vein blood returning to the fetus as unsaturated as the venous blood returning to

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the mother. Were this the case, blood received by the fetus would become progressively less saturated with oxygen as gestation proceeded, and the full-term fetus would be in imminent danger of asphyxiation. Actually this does not happen. The umbilical vein blood has been found to be highly saturated with oxygen in the sheep,[3] and there are reasons to believe the same is true of other animals.[4] One explanation of this lies in an anatomic arrangement of the fetal and maternal capillaries within the placenta. Mossman[5] found that they do not course parallel to one another but actually run in opposite directions. Thus the fetal blood can become equilibrated with that at the arterial end of the maternal capillary bed. A progressive acceleration in rate of flow as gestation proceeds has been reported.[6]

Another mechanism to facilitate oxygen transfer in the placenta has been described. The fetal hemoglobin differs in chemical structure from that of its mother in some species of animals.[7, 8] The difference is such that oxygen is taken up with great avidity by the fetal blood at the low tensions prevailing in the placenta. This mechanism seems to be more important in animals like the ox and sheep, whose placentas present greater barriers to gaseous transfer, than in the carnivores, rodents, and man, with more highly developed placentas.[9]

Although the oxygen capacity of the maternal blood declines as gestation proceeds, reaching about 15.5 volumes per cent at term, that of the fetal blood increases progressively.[10, 11] At full term the human fetus has about 4.5 million red corpuscles per c.mm., but the corpuscles are large; consequently it has 15.5 Gm. of hemoglobin per 100 c.c. and an hematocrit of 51 per cent. Its oxygen capacity is 21.5 volumes per cent.[11] All these factors combine to make it possible to provide the fetus with an adequate supply of oxygen throughout gestation.

Nor is this all there is to the story. Anatomically the fetal heart is so constructed that the most highly oxygenated blood from the placenta becomes shunted first to rostral parts of the body.[13] The umbilical vein blood, rich in oxygen, enters the inferior vena cava and the right atrium of the heart. It traverses the right atrium, where little or no admixture with the venous superior caval stream takes place, and enters the left atrium through the foramen ovale still highly oxygenated. Thus the best blood finds its way to the ascending aorta. It is distributed to the fetal brain and the heart, which is the only organ working as hard in prenatal life as it does after birth.

In prenatal life the need for oxygen is low as compared with the condition after birth. Oxygen consumption is exceedingly slight in early gestation. Toward the latter part of pregnancy the sheep fetus uses oxygen at the rate of about 0.0043 c.c. per gram per minute.[6] A factor of safety exists, for the total oxygen available is more than adequate to meet this need so long as normal healthy conditions prevail in the

placenta. A reservoir of oxygen, in combination with hemoglobin,* is constantly present to provide for minor variation in oxygen utilization. Is this adequate to meet great emergencies? Occlusion of the umbilical cord results in a rapid loss of oxygen from the fetal oxyhemoglobin.[14] The heart slows to conserve the store of oxygen, but the fetal survival time is prolonged far beyond the point at which the blood oxygen is gone. The fetus goes into oxygen debt and apparently utilizes its blood sugar anaerobically with the production of lactic acid, thus prolonging its survival time. Himwich[15] has shown that the survival time of young rats during anoxia can be reduced from fifty minutes to three minutes (the adult survival time) by preventing the utilization of the blood sugar after injections of iodoacetate, and that inhibition of the cytochrome-oxidase system with sodium cyanide does not affect survival. Anaerobic glycolysis appears to be a device insuring survival of the newborn after major crises in the fetal respiratory mechanism during birth.

So far, I have dealt in a general way with chemical factors in fetal respiration. It is likewise important to consider development of the mechanics of breathing. What of the structure and function of the nervous system and the lungs and the question of fetal aspiration of amniotic fluid?

The fetus is capable of performing respiratory movements at an early period. Such activities have been observed during the asphyxia following interruption of its placental circulation as early as the twelfth week.[16] The diaphragm and other respiratory muscles as well as the phrenic nerves have been developed long before this.[17] It is clear that accomplishment of respiratory movements by the fetus awaits further development of the central nervous mechanism, the respiratory center.

To what extent the fetus normally exercises its respiratory mechanism in utero is unknown. Some investigators have held that it does so regularly, at least in the later weeks of gestation. Ahlfeld,[18] a German gynecologist, first reported in 1888 that fetal respiratory movements can be observed directly upon the mother's abdomen. He published convincing graphic records of such activities in a later article.[19] Others, most recently Snyder and Rosenfeld,[20, 21] have confirmed these findings. However, it is only the occasional patient in whom fetal movements resembling respiration are seen. Most patients apparently do not show them; at least, many obstetricians have never seen these movements. It is possible that the movements occur only in individuals in whom there is some condition which jeopardizes the exchange of oxygen and carbon dioxide at the placenta and that consequently they are not representative of the truly normal individual. It is unproved that the movements result in aspiration of amniotic fluid.

*If the fetal blood is 50 per cent saturated with oxygen, and since the total blood volume of the human fetus at birth is about 365 c.c.,[13] there is approximately 40 c.c. of oxygen in the blood (capacity for oxygen = 21.5 volumes per cent).

In order to throw some light on this subject, we have studied prenatal respiratory conditions in experimental animals during the last few years. Only once have we seen fetal movements resembling respirations in an unanesthetized full-term pregnant cat and never in guinea pigs at any stage in pregnancy up to and including labor. We have examined between 100 and 200 pregnant animals. During and following the use of various inhalation anesthetics and after decerebration of the cats, we have encountered rhythmical respirations of the fetuses. We believe that the decreased uterine tone resulting from the anesthetic may have resulted in impairment of an adequate oxygenation of the fetal blood in the placenta and that this caused the movements in question. Near the end of gestation, the fetus has difficulty in maintaining a high saturation of its blood with oxygen under the best of conditions,[3] and it is surprising that fetal respiratory movements are not more frequently encountered.

It is very easy to bring about fetal respiratory movements experimentally. In fact, it is very difficult to avoid them under the usual laboratory conditions of anesthesia and surgical operation. The fetus, apneic in utero, responds to the same stimuli which cause acceleration of respiration in the adult. Carbon dioxide is a potent stimulus. Atmospheres rich in oxygen and containing 8 to 10 per cent carbon dioxide were administered by treacheal cannula to pregnant decerebrated cats.[22] Almost immediately the fetuses began to execute rhythmical respiratory movements. These usually occurred at rates of 60 or less per minute, but at times 120 per minute have been recorded. Atmospheres containing not more than 8 per cent oxygen in nitrogen induced similar respiratory movements. Rebreathing did the same. Any impairment of the placental circulation or of uterine tonus likewise led to respiratory efforts by the fetuses.

We believe that most fetuses are apneic throughout gestation. The fetal respiratory center is insensitive to the level of carbon dioxide prevailing in the blood stream but responds to increases in this level or to anoxia resulting from impairment of the placental exchange. Chemical analyses of the umbilical vein blood of cat fetuses indicate that respiratory movements begin when the oxygen saturation declines to about 50 per cent.[23] In sheep, respiratory movements begin when the venous blood leaves the brain 10 to 25 per cent saturated with oxygen.[24] It is interesting to observe that the incubating chick begins to show respiratory movements in ovo on the seventeenth or eighteenth day.[25] The atmosphere of the air space of the egg over the so-called "avian placenta" (chorioallantois) attains an oxygen content of about 13 to 15 volumes per cent and a carbon dioxide content of 5 to 7 volumes per cent at this time.[26] This is a physiologic condition peculiar to birds. It has no

analogue in mammals, although a physiologic partial anoxemia does develop in late prenatal life as the efficiency of the placenta declines and the fetal oxygen needs increase.

In experiments with guinea pigs and cats, near the end of gestation, two types of fetal respiratory movements have been observed. During mild anoxemia and in decerebrated animals after ether anesthesia, rapid rhythms of shallow movements are seen. These occur with little or no increase in fetal muscle tone (which is decidedly low in utero). When the fetal chest is held between the thumb and finger, practically no expansion can be discerned. These movements can result in aspiration of no great amount of amniotic fluid. After prolonged interference with the placental exchange mechanism and during profound anoxia, another pattern of respiratory movement appears. The shallow rapid rhythms cease, and after considerable squirming and kicking, the fetus begins to gasp rhythmically at rates of 2 to 10 per minute. These gasps are accompanied by a great increase in muscle tonus, and the fetal chest expands strongly. Even in a guinea pig fetus weighing less than 100 Gm. one can scarcely prevent this chest expansion by manual compression. The amniotic fluid can be observed to flow into the nostrils and mouth at each inspiration and to flow out at each expiration.

Aspiration of amniotic contents has been encountered in our experimental animals only under conditions of anoxemia or asphyxia. Some experiments in guinea pigs will serve to illustrate this.[27]

Without using an anesthetic, a thin hypodermic needle was passed through the abdominal wall and into the amniotic sacs of guinea pig fetuses in the last week or two of gestation. Small quantities of fluid were withdrawn (0.4 c.c. to 1 c.c.) from the region about the nostrils and replaced with colloidal solutions of thorium hydroxide (thorad) or dioxide (thorotrast). In twenty-seven fetuses so treated, a large series of x-ray films exposed after various intervals up to fourteen days failed to show lung shadows which would signify that the fetuses had aspirated this radiopaque material. The fetuses swallowed and the thorotrast or thorad appeared in the fetal stomach and intestines regularly.

Twenty-five additional experiments were performed. Films exposed after these injections likewise showed no aspiration by the fetuses. The pregnant guinea pigs were then allowed to breathe atmospheres low in oxygen or high in carbon dioxide, or to rebreathe air until anoxemia had set in. Fetal respiratory movements could be observed in a number of these specimens. X-ray films were exposed subsequently. Of fourteen experiments showing shallow, questionable, or no fetal respiratory movements, only two films revealed thorotrast in the fetal respiratory tract. In the remaining twelve experiments, all showing strong respiratory movements, seven positive results were obtained. In addition, three other fetuses dying in utero at about the time of labor or otherwise

asphyxiated at birth showed lungs well filled with thorotrast in consequence of fetal aspiration of the amniotic contents.

These experiments reveal another point of some importance. The lungs of the fetuses which aspirated thorotrast or thorad during experimental anoxemia were not completely filled with this material. Only the major branches of the respiratory tree contained it. But those dying asphyxial deaths showed thorotrast throughout the entire lung, in alveoli as well as in bronchioles. This indicates that intrauterine respiratory movements of the guinea pig are not always effective; they do not result in expansion and in the filling of the fetal lungs with amniotic fluid unless they are in the nature of deep gasps.

Recently we have studied the structure of fetal lungs with this point in mind.[28] We opened the abdomen of the pregnant guinea pig after local infiltration of procaine. A clamp was placed on the neck of a full-term fetus without opening the uterus, and the specimen was fixed in situ in formalin. Histologic study of the lungs revealed that they were truly atelectatic. They presented a compact glandlike appearance; bronchi and bronchioles had definite lumens, but the more distal passages and alveoli were collapsed. This picture has not been observed in human stillborn lungs at term and for the probable reason that the fetuses aspirate quantities of fluid during marked respiratory efforts at the time they die in utero.

In other guinea pigs we clamped the necks of the fetuses only after they had been observed to gasp and to inspire the amniotic fluid during asphyxia induced by occluding the uterine blood vessels. Lungs of these specimens resemble human stillborn lungs. Alveoli have been opened by the aspiration of amniotic fluid.

Guinea pigs which were born normally were allowed to breathe air for various periods of time. The tracheas were then clamped during inspiration and the lungs fixed in situ. After five minutes of breathing the lungs were only partially expanded. The unexpanded parts were compact and glandlike. They resembled the truly atelectatic fetal lung.

From these experiments we conclude that the guinea pig fetus does not aspirate its amniotic fluid normally. Intrauterine respiratory movements cause aspiration of significant quantities of fluid only when they become deep gasplike inspirations. Such movements come about during asphyxia but are not found under normal conditions.

To summarize, it is becoming evident that the physiology of respiration in utero is not so greatly different as it might seem from that of the newborn infant or even of the adult individual.

Early in embryonic life the part of the somatic motor system which is to be concerned with breathing later on has its genesis. Soon higher neurons are formed and are brought into a mutually integrated aggregate to comprise a respiratory center connected with the somatic motor system. Appropriate stimulation, by afferent nervous discharge into the

center, by the chemical agent carbon dioxide acting upon it directly, or by anoxial elevation of its excitability, can bring it into premature activity. But it is doubtful if this newly formed respiratory mechanism actually functions in the strictly normal course of intrauterine existence. The respiratory mechanism of the fetus seems to be a dormant system, charged with potentialities long in advance of the time it can be of any use to the fetus. Premature birth finds the new individual well prepared in respect to its respiratory system.

Under experimental conditions it is very easy to alter the physiologic state of the fetus in utero and to start respiratory movements. Partial anoxemia usually results in heightened excitability of the fetal respiratory center, and its neurons begin to discharge in response to the usual factors which are stimulatory in the adult.

Respiration begins at birth, because the excitability of the center increases as anoxemia builds up during placental separation. The heightened blood carbon dioxide and the afferent stimuli from the changed environment are important factors. If the excitability of the respiratory center is unimpaired by narcotics and anesthetics, breathing begins at once.

Rhythms of shallow rapid respiratory movements which are occasionally seen late in gestation signify that the fetus is momentarily experiencing an elevation of excitability of its center, or an elevation of blood carbon going to the brain. A physiologic partial anoxemia may occur toward the end of gestation as the result of progressive decline of placental efficiency; with this, minor rhythms of fetal respiratory movements like those recorded by Ahlfeld are occasionally seen. However, even these shallow rapid respiratory movements are rarely encountered, and when observed, should give cause for apprehensiveness on the part of the obstetrician, for they are a sign of anoxemia and may warn of impending danger of fetal asphyxia.

That intrauterine respirations are uncommon depends upon the fact that the blood the fetus receives from the placenta is rather well saturated with oxygen, and this blood is shunted through the fetal heart and directly to the brain, so that anoxia of the respiratory center is avoided.

Aspiration of amniotic fluid is not a normal phenomenon. It occurs only under conditions of marked anoxia. Fortunately for the fetus, a wide margin of safety is provided against the danger of "drowning" in its amniotic fluid.

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NEUROTROPIC VIRUS DISEASES OF MAN

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IN THE short space of time available for this discussion I shall attempt no more than a brief résumé of some of the present knowledge of the neurotropic virus diseases of man. It seemed to me worth while to survey the diseases of the human nervous system which are presumed or known to be caused by viruses, to examine in brief the distinguishing properties of the known viruses, and then to touch upon a few of the problems which confront the investigator of the neurotropic virus diseases of man.

In attempting to organize our present knowledge into some logical pattern, it seemed convenient to divide the neurotropic virus diseases of man into epidemic and nonepidemic groups (Table I). In the epidemic group we find poliomyelitis, about which no more need be said at this point, and encephalitis. Epidemic encephalitis, first noted as a clinical entity in 1916 and 1917, has been differentiated since into a variety of distinct diseases which have in common only the fact that they occur in epidemics and that the central nervous system becomes the seat of a diffuse nonsuppurative encephalitis. The five distinct varieties of epidemic encephalitis can be differentiated from one another on clinical, epidemiologic, or biologic grounds.

The encephalitis lethargica, or von Economo type, which flourished between 1916 and 1926 and has not occurred in epidemic form since, was world-wide in distribution, occurred predominantly in the winter months, attacked chiefly adolescents and young adults, and was associated with a death rate which did not exceed 10 to 20 per cent. There was a high incidence of chronic, disabling sequelae. Although the pathology of this form of encephalitis is entirely compatible with virus etiology, the etiologic agent remains unknown, and the results of neutralization tests with convalescent sera indicate that it is different from the known encephalitis viruses.

The St. Louis type of encephalitis, observed since 1932 and recognized as a clinical and biologic entity in 1933, is known to exist only in certain regions of the United States, occurs during the hot summer months, attacks predominantly persons beyond middle age, and is associated with a death rate of about 20 per cent. There is usually rapid and complete recovery of the survivors. The virus thus far has been demonstrated in the nervous system but not in the blood or spinal fluid

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of human cases. In survivors the diagnosis of this form of encephalitis can be made only when it can be shown that neutralizing antibodies which were absent during the acute stage appeared during convalescence. The mode of transmission of the virus and the origin of epidemics are unknown. During interepidemic years in St. Louis there have been cases of encephalitis which clinically and pathologically were indistinguishable from the epidemic form, but no virus could be isolated from them post mortem, and no neutralizing antibodies were present in the convalescents.

TABLE I

NEUROTROPIC VIRUS DISEASES OF MAN

EPIDEMIC	NONEPIDEMIC
Poliomyelitis	Lymphocytic choriomeningitis
Encephalitis	Pseudolymphocytic choriomeningitis
Lethargica (von Economo)	Western equine encephalitis
St. Louis	Rabies
Japanese type B	Louping ill
Eastern equine	"B" virus disease
Australian "X"	Herpes simplex
	Herpes zoster
	Acute nonsuppurative encephalitis (of unknown etiology)
Postinfection encephalitis: measles, varicella, vaccinia, mumps, etc.	

The Japanese type B encephalitis has been known in Japan for many years as a clinical entity called "summer encephalitis," but the first large epidemic occurred in 1924, and there has been a number of others since then. The virus was isolated and identified in 1934 and 1935 and has been found in the blood and spinal fluid as well as in the nervous tissue of human cases. Epidemics of this form of encephalitis thus far have been limited to Japan, although the disease has recently been identified in a sporadic case in the part of China occupied by the Japanese. The disease occurs during the hot summer months, and in most outbreaks persons in the older age groups predominantly are attacked; in 1935, however, more than 40 per cent of the cases occurred among children in the first ten years of life. The death rate frequently exceeds 50 per cent, and rapid recovery is usual among the survivors. There is evidence that the disease may be transmitted by mosquitoes.

The eastern equine type of encephalitis thus far has been recognized in a single epidemic which occurred in the state of Massachusetts in August and September of 1938. It occurred during the course of an extensive epidemic among horses in the same area. Seventy per cent of the forty-six human cases occurred in infants and children under 10 years of age. About 70 per cent of the patients died during the Massachusetts epidemic, and some of the survivors have shown sequelae such as paralysis and mental changes.

The virus of eastern equine encephalomyelitis has been found in nature in the horse, mule, pheasant, and pigeon and is primarily a

disease of these and other lower animals rather than of man. Existing data point to transmission by the bite of the Aëdes type of mosquitoes. In the 1938 epidemic most patients had no contact with the horses, and many were never closer to them than two or three miles. The virus is present in the blood of most infected animals but usually only before the onset of nervous signs. It has been isolated from the nervous tissue of human beings, but not from the blood or spinal fluid of the few patients in whom they were tested. Neutralizing antibodies for this virus appear relatively early and have been detected in man as early as the sixth day.

Australian "X" disease refers to a form of encephalitis which occurred in Australia in 1917 and 1918, and again in milder form in 1922 and 1926. The clinical course and death rate of 70 per cent differentiated it at the time from the von Economo type of encephalitis. Although the virus that was isolated was lost before complete studies on it had been made, its pathogenicity for sheep places it in the group with the viruses of Japanese B encephalitis and of louping ill, a disease of sheep in Northern England and Scotland. However, since the louping ill virus is not known in Australia and its insect vector is absent, since the known infections with this virus have occurred only in laboratory workers, all of whom have recovered although the mortality of Australian "X" disease was 70 per cent, and since the serum of at least one Australian "X" convalescent, admittedly of ten years' standing, failed to neutralize the louping ill virus, it is now assumed that the Australian "X" disease was either identical or closely related to the Japanese type B encephalitis.

It is apparent from this brief review that with the exception of the von Economo type of encephalitis the other epidemic neurotropic virus diseases of man all have been successfully transmitted to animals, and the causative viruses have been submitted to more or less detailed study of their properties. Although in addition to the viruses responsible for the epidemic diseases, seven other viruses are known to have caused disease of the human nervous system, the etiology of the bulk of the sporadic cases of nonsuppurative encephalitis and meningitis remains obscure.

Among the seven viruses in the nonepidemic group which are known to affect the human nervous system, all but the herpes simplex virus represent infectious agents whose natural habitat is in lower animals. The virus of lymphocytic choriomeningitis, which has been proved to be the etiologic agent in at least some of the cases of acute aseptic meningitis, has been found to be carried by mice, dogs, guinea pigs, and monkeys. The recent finding of the virus in a large proportion of wild mice trapped in the homes of patients with lymphocytic choriomeningitis and its relative absence in other homes of the same region serves to emphasize the possible role of mice in the transmission of the

disease to human beings. Whether or not this virus may be the cause of certain cases of encephalitis, some of which may be fatal, as has been suggested by some recent findings, cannot be established unequivocally until more work has been done. This virus, however, produces primarily a systemic disease with secondary localization in the nervous system. From the experiments carried out in France on human beings inoculated with mouse virus, it is known that an influenza-like syndrome may be the only result of infection with the virus, and the finding of neutralizing antibodies in 11 per cent of 2,000 sera collected at random in the United States suggests that in its nonmeningeal form, the disease may be widespread and unrecognized. A specific diagnosis can be made by isolating the virus from the blood or spinal fluid and by demonstrating that complement-fixing or neutralizing antibodies which were absent during the acute phase had made their appearance in convalescence.

The virus of pseudolymphocytic choriomeningitis was reported in 1939 as having been isolated from two human beings, one with meningitis, and the other with mild encephalitis. It can be differentiated from the lymphocytic choriomeningitis virus by its larger size as well as its immunologic distinction.

The virus of western equine encephalitis has been shown to be the cause of a number of sporadic cases of encephalitis in children and adults residing in the western part of the United States.

Rabies, which is perhaps the oldest recognized neurotropic virus disease, continues to present new problems. The demonstration in Trinidad and South America that bats and rats may harbor and transmit the virus without themselves succumbing to the disease has introduced new epidemiologic considerations. The reinvestigation of the whole problem of vaccination in recent years, while failing to confirm Pasteur's experiments on the immunization of dogs following rabic infection and bringing to light that many rabies vaccines completely fail to immunize at any time, nevertheless has led not only to an appreciation of what may be expected from good vaccines, but also to the development of methods by which the quality of such vaccines may be assayed and assured.

Louping ill is a tick-transmitted disease of sheep in Northern England and Scotland. While it has not been discovered thus far among sheep herders or others attending sick sheep, five laboratory workers studying the virus in mice became infected. All five exhibited varying degrees of encephalitis but recovered and subsequently showed neutralizing antibodies against the virus.

"B" virus is the name given to a virus isolated from the viscera and nervous system of a laboratory worker who died of an ascending myelitis following the bite of an apparently normal monkey. This virus is now known to be harbored by monkeys which may show no apparent signs of disease. Two other fatal cases of encephalomyelitis following monkey bites, one in another laboratory worker in Baltimore, and the other in a

former king of Greece, are also on record. The "B" virus belongs to a family of viruses of which the herpes simplex virus of man and the pseudorabies virus of pigs and cattle are also members.

The inclusion of herpes simplex in this list may perhaps be questioned by some. It is included in this group, however, not only because it has the capacity of invading the central nervous system and producing a fatal encephalomyelitis in animals, but also because there is more than suggestive evidence that even in human beings it may occasionally wander beyond the skin and mucous membranes. The demonstration that it may be present in the human gasserian ganglia raises the question of the possible role of the herpes simplex virus in some cases of trigeminal neuralgia.

Although the pathology of herpes zoster is entirely compatible with a virus etiology, all attempts to isolate the infectious agent and transmit it to animals have thus far been unsuccessful. However, various experiments carried out on human beings and certain serologic reactions between the vesicular contents and convalescent sera strongly suggest that herpes zoster and varicella perhaps may be manifestations of the same virus.

It is pertinent to note at this point that when all the known viruses which have been found to affect the human nervous system are accounted for, one is still confronted with the fact that in most of the sporadic cases of acute nonsuppurative encephalitis or aseptic meningitis the etiologic agents are as yet unknown. It is perhaps comforting to realize, therefore, that with the exception of the viruses of poliomyelitis, rabies, and herpes simplex, all the others have been isolated, recognized, and identified in the past five to ten years.

The postinfection group of encephalitides, occurring during the course of certain systemic virus diseases such as measles, varicella, vaccinia, mumps, etc., as well as after other infections and after rabies vaccination, while still but incompletely understood appears to differ from the neurotropic virus diseases in that the white matter is affected chiefly in the form of widespread perivascular demyelinization and that the etiologic relationship of any virus to these lesions has not been established as yet. While it is sometimes stated that the meningoencephalitis of mumps is caused by the recently isolated virus of mumps, it still remains to be shown that this virus is present in the nervous system.

The eleven viruses known to affect the human nervous system are as distinct and different from one another as are the tubercle bacillus, typhoid bacillus, pneumococcus, streptococcus, etc., and can be identified with as much certainty. Aside from the fact that they are all immunologically distinct, identification can be accomplished in most instances by determining whether or not the unknown virus can produce disease in rhesus monkeys, mice, guinea pigs, and rabbits, by estimating its approximate size from its capacity to pass certain filters, and by the

type of change it produces in infected cells. These properties are summarized in Table II. It will be noticed that the determination of the

TABLE II

SOME PROPERTIES OF VIRUSES AFFECTING THE HUMAN NERVOUS SYSTEM

VIRUS	PATHOGENICITY FOR USUAL LABORATORY ANIMALS*				APPROXIMATE SIZE (mμ)	INCLUSIONS
	RHESUS MONKEYS	MICE	GUINEA PIGS	RABBITS		
Poliomyelitis	+	0	0	0	10	Intranuclear; type B
Encephalitis (St. Louis)	0 to ±	+	0	0	25	0
Encephalitis (Japanese)	+	+	0	0	Small	0
Louping ill	+	+	0	0	17	0
Lymphocytic choriomeningitis	+	+	+	0	50	0
Pseudolymphocytic choriomeningitis	+	+	0 or ±	0	185	0
Equine encephalitis (eastern)	+	+	+	+	25	Intranuclear; type B
Equine encephalitis (western)	+	+	+	+	25	Intranuclear; type B
Rabies	+	+	+	+	125	Cytoplasmic; Negri bodies
"B" virus	+	0 to ±	0 to ±	+	125	Intranuclear; type A
Herpes simplex	0	+	+	+	125	Intranuclear; type A

*The pathogenicity indicated in this table is for the viruses as they are found in human tissues, body fluids, secretions, or excretions.

pathogenicity of a virus for a given number of animals is used in the same manner and is just as helpful for purposes of identification as is the determination of the types of culture media upon which unknown bacteria will grow. Thus, it can be seen that when an unknown virus is found to be pathogenic for monkeys but not for mice, guinea pigs, or rabbits, it corresponds in its properties to the virus of poliomyelitis. When the virus is pathogenic for rhesus monkeys and mice but not for guinea pigs and rabbits, the viruses of St. Louis encephalitis, Japanese encephalitis, and louping ill come up for consideration; of course, while the St. Louis virus produces only a mild disease in monkeys, and that irregularly, and while it is not pathogenic for sheep, as are the other two, it would be necessary nevertheless to resort to immunologic tests for the differentiation of the viruses in this group. The viruses of lymphocytic choriomeningitis and pseudolymphocytic choriomeningitis are the only ones in this group which are pathogenic for monkeys, mice, and guinea pigs, but not for rabbits. Because of the considerably larger size of the pseudolymphocytic choriomeningitis virus, rapid differentiation could be made by filtration through a suitable Berkefeld "N" or "W" filter when carefully calibrated gradocol membranes are not available. Only three of the viruses, eastern and western equine encephalitis

and rabies, are pathogenic for all four animals, but the rabies virus could quickly be differentiated not only by the presence of Negri bodies, but also by its larger size, which would cause it to be held back by filters through which the equine encephalitis viruses would readily pass. Finally, the herpes simplex and "B" viruses can be distinguished from all the others by the type A intranuclear inclusions which develop in the infected cells and from one another by the fact that the former is not pathogenic for rhesus monkeys while the latter, i.e., "B" virus, is.

As has already been pointed out, these eleven viruses account for all the known epidemic virus diseases of the human nervous system with the exception of the von Economo type of encephalitis, which is probably only temporarily quiescent, and for only a small fraction of the large number of the sporadic ones. Therefore, one of the important problems, still facing investigators of this group of diseases is the search for the as yet undiscovered infectious agents, and, perhaps I may be forgiven for venturing a guess that little additional progress will be made in this direction until hitherto unused animals are found for which the unknown viruses may have special affinities. However, equally important with the task of discovering the as yet unknown viruses is the problem of obtaining a better knowledge of the natural history of the diseases whose causative agents are already well known. For even as regards the well-studied epidemic group of diseases, we still have no answers for the basic questions concerning the reservoirs of virus, the modes of transmission, the precise nature of these diseases in man, the factors of individual susceptibility or resistance, and, therefore, no sound conception of measures for prophylaxis or treatment. It is only by painstakingly acquiring this knowledge that one may hope to find the weak spot in the armor of each disease and ultimately bring it under control.

CONGENITAL HEART DISEASE AND THE ELECTROCARDIOGRAM

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THE application of electrocardiography in the more accurate diagnosis of congenital heart conditions increases yearly in scope and significance. Schnitker[1] mentions that Einthoven employed the electrocardiograph in congenital heart disease as early as 1908, five years after he first introduced the instrument for clinical use. Thomas Lewis,[2] by 1918, had already recognized major facts concerning electrocardiographic findings in congenital heart disease, such as the inversion of all the summits in the first lead in dextrocardia, marked right axis preponderance in congenital pulmonary stenosis, exaggerated amplitude of QRS complexes in several leads as a valuable sign of the possibility of a congenital heart condition, and the occurrence of a normal tracing in uncomplicated patent ductus arteriosus. By 1925, Alexander and his associates[3] related abnormally large P waves in Leads I or II, or both, with congenital pulmonary stenosis as well as acquired mitral stenosis.

More recently, in 1937, Drawe and co-workers[4] reported that children with congenital pulmonary stenosis or tetralogy of Fallot quite frequently showed changes in the electrocardiogram, whereas those with interventricular septal defect or patent ductus arteriosus had tracings rarely deviating from normal. In the same year, Wachtel and Katz[5] called attention to the occurrence of widely diphasic QRS complexes in electrocardiograms of individuals with congenital heart disease. The most significant and recent contribution relating to the electrocardiogram in congenital heart disease is Schnitker's monograph,[1] a study of 109 cases, 106 with autopsy.

Our study is presented with the view of further crystallizing, if possible, the observations made in the past few years on electrocardiography in congenital heart disease. It differs from Schnitker's in that practically all of the children discussed in this report are living. We recognize full well that our diagnoses in some instances may be incomplete, or inexact, due to multiple defects in the heart. The criteria on which diagnoses are made in each group of cases are described.

THE NORMAL ELECTROCARDIOGRAM IN THE CHILD

To understand the changes found in the electrocardiograms of children with congenital heart conditions, it is necessary to become familiar with tracings recognized as normal. Table I includes information available to establish the normal tracing in the child. The table is based on

From the Cardiac Service of Children's Memorial Hospital.
This study was aided by the Bachmann Memorial Fund.

TABLE I

COMPARISON OF THE NORMAL ELECTROCARDIOGRAPHIC FINDINGS OF A CHILD WITH THOSE OF THE ADULT

	P WAVE		QRS COMPLEX		T WAVE	
	CHILD	ADULT	CHILD	ADULT	CHILD	ADULT
Lead I	Higher than in adult Height: 0.2 to 1.5 mm. Upright	Upright			Upward	Upward
Lead II	Equal to adult Height: 0.2 to 2.7 mm. Upright	Upright			Upward	Upward
Lead III	14 per cent downward or diphasic Height: -1.5 to 1.5 mm.	Occasionally diphasic or downward			About 20 per cent downward. Usually higher than in adults	Upward, diphasic or downward
Form	15 per cent notched	30 to 35 per cent notched	33 per cent diphasic QRS in Lead I (ratio less than 1:4). Vibratory types ("M-" or "W-" shaped complex) not unusual, especially in Lead III	Vibratory QRS complexes not abnormal in Lead III		
Duration	Not more than 0.09 sec.	Not more than 0.1 sec.	Not more than 0.09 sec.	Not more than 0.1 sec.		

	CHILD	ADULT
Rate	From 3 to 14 years: range, 164 to 52	
P-R interval	0.08 to 0.18 sec.; occasionally up to 0.20 sec.	0.12 to 0.20 sec.
Axis deviation	Right axis deviation normally present for the first three months of life, with noticeable decrease at 4 to 6 months of age Left axis deviation occurs in about 7 per cent of average healthy children. Usual axis deviation is 20 to 105°.	

one given by Pardee[6] for adults and is expanded to include facts about children from other sources.[7, 8, 9] The diphasic QRS complex found in the tracings of about one-third of the normal children does not have the wide or bizarre swing of QRS complexes found in the electrocardiograms of children with certain kinds of congenital heart disease. Normally, vibratory QRS complexes are more often present in the third lead and are associated frequently with downward T waves.

INTERVENTRICULAR SEPTAL DEFECT

Defects of the interventricular septum occur most frequently at the base of the ventricle, the perforation lying usually just beneath the aortic valve. It may vary in size from a pinhead to an inch or more in diameter. The diagnosis of this most commonly encountered congenital heart defect is usually not difficult. The child with an uncomplicated interventricular septal defect is generally without symptoms of heart disease. The harsh systolic precordial murmur, sometimes accompanied by a systolic thrill, is usually loudest in the left third and fourth interspaces. The great danger of the condition is not from the influence of the lesion itself, but from its frequent association with subacute bacterial endocarditis. The x-ray, if characteristic, gives a globular shaped heart, with some increase in the transverse diameter, although most frequently the x-ray shadow of the heart cannot be distinguished from normal.

Case Reports (Fig. 1):*

CASE 1.—G. A., a girl aged 12 years, was known to have had a heart condition before coming to us at 5 years of age. She was without symptoms. There was an intense basal systolic murmur, maximum in the third and fourth left interspaces. A coarse thrill was palpable. The electrocardiogram showed nothing unusual. The QRS complex was vibratory in Lead III.

CASE 2.—B. B., a girl aged 4½ years. Heart condition was recognized at the age of 1 month. No cyanosis was present at birth or when the child was first seen. Only at the age of 3 months had she had several short spells of blueness, but there had been no recurrence of cyanosis since that time. Her nutrition was satisfactory. She had a harsh systolic murmur maximum in the fourth interspace at the left sternal margin. The x-ray showed a heart about 10 per cent enlarged, but of normal contour. The electrocardiogram showed the P-R interval to be 0.16 second and the QRS complexes in Leads I and II to be widely diphasic.

CASE 3.—D. McG., a girl aged 3½ years. A murmur was discovered when she came to the clinic for tonsillectomy. There was no history of cyanosis, and nutrition was good. She had a harsh precordial systolic murmur heard loudest in the fourth interspace to the left of the sternal margin. A thrill was palpable in the left fourth interspace near the sternal margin. X-ray showed no enlargement, and the electrocardiogram was normal in appearance.

CASE 4.—R. G., a boy aged 7 years, at 18 months of age was known to have a heart murmur. Nutrition was good, and there was no cyanosis. He had a localized

*The QRS complexes were retouched in all illustrations so that the peaks could be seen more readily.

rough murmur in the second and third left interspaces, with a faint thrill felt over the precordium. X-ray showed a heart normal in size and contour. The electrocardiogram revealed a P-R interval of 0.2 second.

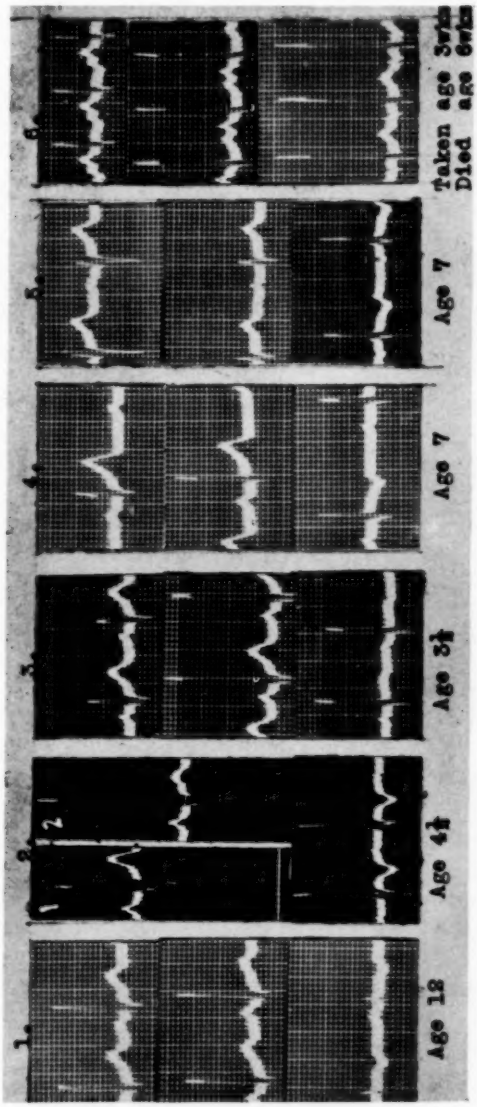

Fig. 1.—Interventricular septal defect.

CASE 5.—R. M., a boy aged 7 years was known to have had congenital heart since the age of 6 months. He was never cyanotic. He was thin and rather pale, without cardiac symptoms. There was a harsh systolic murmur at the left sternal

border in the second, third, and fourth interspaces. The x-ray showed general enlargement, slightly more to the left. The electrocardiogram showed a P-R interval of 0.18 second and definite right axis deviation.

CASE 6.—This is an autopsied instance of interventricular septal defect recognized during life by the characteristic basal systolic murmur. The defect was 3 mm. in diameter at its widest point. The baby had the tracing taken when he was 3 weeks old. He died at the age of 6 weeks of pneumonia and septicemia. He was brought to us because of numerous serious congenital deformities of the extremities, such as syndactylism and shortness of the legs due to bony deformities. X-ray showed that the heart was generally enlarged by approximately 20 per cent. Electrocardiogram showed nothing unusual.

Comment.—In singling out the significant findings in the six electrocardiographic tracings in Fig. 1, which deserve comment, there are only the widely diphasic QRS complexes in Leads I and II (Case 2), the P-R interval of 0.20 second (Case 4), and the right axis deviation (Case 5). Even if the increased P-R interval and the right axis deviation are due to the congenital heart conditions, these findings have no differentiating qualities for congenital heart disease. By far the most characteristic finding of congenital heart disease is the widely diphasic or bizarre QRS complexes of Case 2. Of the instances of interventricular septal defects presented, only this case gave a history of cyanosis at one time, and this indicates that it probably is the most serious of the interventricular septal defects presented. The relationship between widely diphasic QRS complexes or bizarre QRS complexes and marked congenital heart conditions will be discussed at greater length under comments on tetralogy of Fallot.

One may conclude that the usual uncomplicated instance of interventricular septal defect, as a rule, gives a normal electrocardiographic tracing. This contention is supported by Drawe, Hafkesbring, and Ashman.[4]

SUBAORTIC STENOSIS

Subaortic stenosis is one of the less common of the congenital heart conditions. As a rule it is compatible with long life and does not give rise to cardiac symptoms. Cyanosis is absent. The child's exercise tolerance is practically always normal, and the nutrition of the child is good. A harsh systolic murmur in the second right interspace and a palpable thrill in the first and second right interspaces and in the suprasternal notch are usually present. The heart size is not enlarged enough to determine clinically; and although the apex beat is of normal or increased intensity, the pulse is weak in quality. The blood pressure is low and the pulse pressure smaller than normal. Usually the x-ray indicates a heart shadow 10 to 20 per cent enlarged, with an aortic configuration.

Case Reports (Fig. 2):

CASE 1.—T. M., aged 9 years, came to us first at the age of 6 years, with a history of a recognized heart condition from birth. He was fairly well developed and

was without cardiac symptoms of any kind. On percussion the heart was not found enlarged; there was a palpable thrill in the suprasternal notch and the first right interspace. There was a precordial murmur heard loudest in the second right interspace. The blood pressure was 80/54. The x-ray showed a heart 20 per cent enlarged, with an aortic configuration. No unusual findings appeared in the electrocardiogram.

CASE 2.—H. A., aged 10, is a boy whom we have known since he was 4. He was of normal nutrition but did complain of tiredness. He had never been cyanotic. He had a harsh basal systolic murmur loudest in the second right interspace. There was a thrill in the suprasternal notch and the second right interspace. The blood pressure was about 90/70. On x-ray the heart was enlarged about 10 per cent. The electrocardiogram showed no unusual findings.

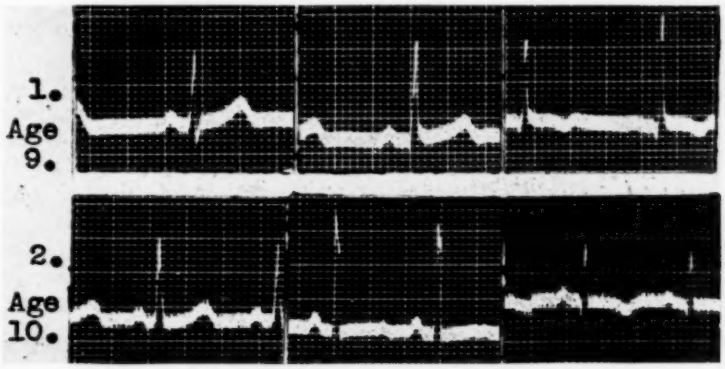

Fig. 2.—Subaortic stenosis.

Comment.—The diagnosis of subaortic stenosis must be made clinically. The nature of the lesion is such as to make one believe that a left axis deviation would be encountered in the electrocardiogram, but here in two instances there is no left axis deviation. This finding might, perhaps, develop later in life. The electrocardiographic tracings in these and in all our other instances of subaortic stenosis are normal in appearance.

PATENT DUCTUS ARTERIOSUS

Patent ductus arteriosus, as a rule, is not difficult to diagnose. The murmur of this lesion is one of the most characteristic of all sounds. Its continuous, cyclic nature has been variously described as a "coffee-mill," "machinery," or "humming-top" murmur. In very young children, the diastolic element of the murmur is not always fully developed, but its location and possibly a thrill rather sharply limited to the second and third left interspaces should aid in the diagnosis. The rather sharp localization of the murmur and thrill sometimes makes them easily overlooked in milder instances for a while. To avoid this, the base of the heart should be listened to as routinely as the apex.

There are likely to be subjective symptoms from this lesion. Tiring with moderate exercise often occurs. Paleness may be present, but not cyanosis. There is usually no history of cyanosis at birth. The x-rays in these cases are reported as showing heart shadows 15 to 25 per cent enlarged. Prominence of the pulmonic cone is a significant finding, but is not always present. The sphygmomanometer usually gives a high pulse pressure reading.

Case Reports (Fig. 3):

CASE 1.—M. M., a girl aged 7 years, was found to have a congenital heart defect at the age of 1 month. Although well nourished, the child was pale. She tired easily with exercise. There was a humming-top murmur and a thrill maximum in the left second and third interspaces. X-ray showed 20 per cent enlargement of the heart, mostly to the left, and electrocardiogram revealed no abnormalities.

CASE 2.—A girl, aged 6½ years was known to have had a congenital heart condition since the age of 10 months. She fatigued easily and was rather thin. The heart was slightly enlarged on percussion. A machinery murmur and a thrill were maximum in the second left interspace. The heart was approximately 15 per cent enlarged, but of normal contour, with no unusual electrocardiographic findings.

CASE 3.—N. K., a girl aged 7 years, was brought to us at 22 months of age, rather pale and undernourished. There was no history of cyanosis. She had humming-top murmur and a thrill maximum in the second left interspace. X-ray of the heart showed 25 per cent enlargement. The electrocardiogram showed diphasic QRS complex in Lead I.

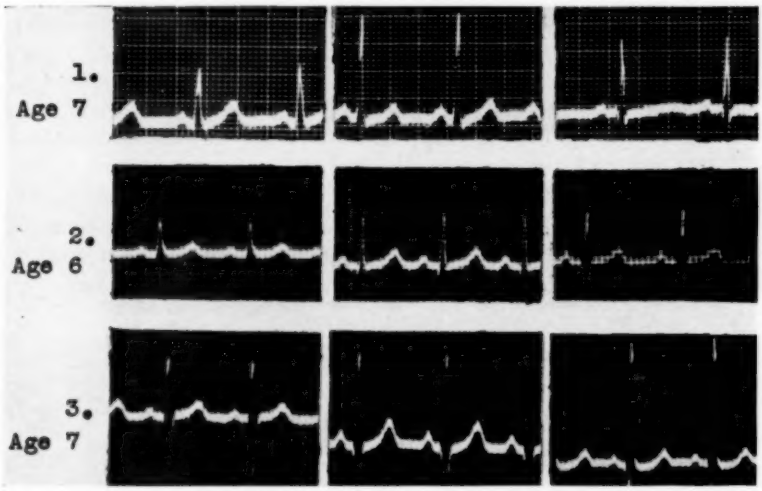

Fig. 3.—Patent ductus arteriosus.

Comment.—The diagnosis of patent ductus arteriosus is generally simple after one has experienced hearing its very characteristic murmur. Difficulty in diagnosis may arise early in life, in certain instances, before the murmur assumes its two-phase character.

It is surprising in view of the presence of symptoms such as fatigue on exertion, as well as the x-ray findings of moderate enlargement of the heart, that the electrocardiograms are so distinctly normal. In the tracings we show, there is a diphasic QRS in the first lead of the third tracing, but this diphasic QRS is probably a normal finding because it is not of abnormally wide excursion. Drawe and associates,[4] in tracings of ten cases of patent ductus arteriosus, found that only one had suggestive findings of myocardial disease.

Gross,[10] in discussing the instances of patent ductus arteriosus which may be considered for operation of the lesion, warns against those cases which show an abnormal electrocardiographic tracing. We fully agree that abnormalities in a tracing should seriously raise the question of associated lesions with the patent ductus arteriosus.

COARCTATION OF THE AORTA

Coarctation of the aorta of the adult type is a sharp constriction of the aorta in the region of the insertion of the ductus arteriosus, giving rise to collateral vessels for supplying the circulatory needs of the body below the point of narrowing of the aorta. This condition is usually compatible with an active, normal existence for three or more decades, but prognosis must always be guarded.

We consider this congenital lesion much more common than is generally recognized. It is overlooked during childhood because the so-called classical signs by which the diagnosis can be easily made, namely, tortuous, pulsating collateral vessels visible on the walls of the chest and erosion of the ribs seen in the x-ray, are almost invariably absent in young children. Often these findings do not appear until the second to the fourth decades of life.

Most of our cases were discovered by noting the absence or weakness of femoral pulsations in children with distinct heart murmurs. One or two were discovered because of the fairly characteristic high blood pressure readings in the arms.

In a child with a distinct heart murmur, the syndrome of weak or absent femoral pulsations, inability to get blood pressure readings in the legs, or the obtaining of lower readings in the legs than those in the arms (which is the reverse of normal), and usually elevated blood pressure readings in the arms, is pathognomonic of coarctation of the aorta.

Case Reports (Fig. 4):

CASE 1.—J. K., aged 10 years. The patient's mother wanted him to have a tonsillectomy because of frequent colds. He was a well-developed boy without cardiac symptoms. He had a short, harsh basal systolic murmur. Blood pressure reading in the left arm was 158/116; right arm, 152/90; left leg, not obtainable; right leg, not obtainable. He had no femoral pulsations and no pulsation of intercostal arteries. The x-ray showed a heart 20-per cent enlarged, definite narrowing of the aortic arch, but no erosion of ribs. The electrocardiogram showed a marked left axis deviation.

CASE 2.—J. G., aged 10 years, was known to have a congenital heart condition, but the exact nature of the condition was overlooked until recently. He was a small, slender, apparently well boy, with a rough basal systolic murmur best heard in the first and second right interspaces. His blood pressure readings were: left arm, 120/90; right arm, 110/70; left leg, not obtainable; right leg, not obtainable. His femoral pulsations were not palpable, as contrasted with those of his brother just one year younger and of about the same size and weight. The x-ray showed no erosion of the ribs, and the electrocardiogram was normal in appearance.

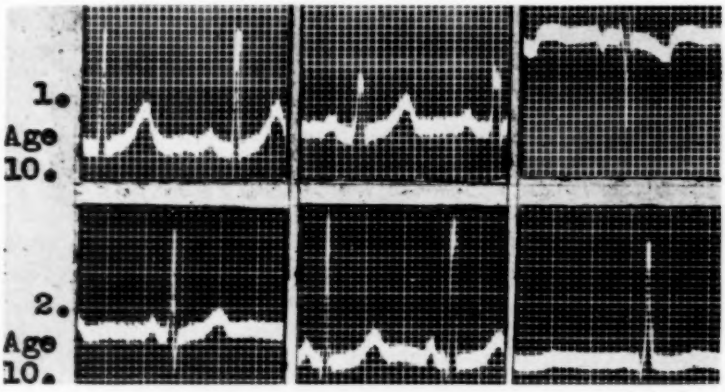

Fig. 4.—Coarctation of the aorta.

Comment.—The diagnosis of coarctation of the aorta in children does not depend upon the electrocardiographic tracing, and the x-ray is often negative. The clinical findings, combined with the realization that it is a not uncommon type of congenital heart condition, will render a correct diagnosis nearly every time.

In general, the presence of a coarctation gives rise to a left axis deviation, but there may be no axis deviation shown in the electrocardiogram. The degree of left axis deviation is probably influenced by the degree of constriction of the aorta and the age of the individual.

TETRALOGY OF FALLOT

Congenital heart conditions which are hardest to diagnose properly are the cyanotic ones. We find that clinically we cannot distinguish too accurately all the congenital heart conditions causing cyanosis.

One of this group is tetralogy of Fallot. The basic lesion of the tetralogy is a pulmonary stenosis associated with a defect of the interventricular septum, dextroposition of the aorta, and right ventricular hypertrophy. Since the tetralogy of Fallot is the most common congenital heart condition with cyanosis permitting survival beyond infancy, it should be thought of first. A rough precordial systolic murmur in a child who is moderately comfortable despite the cyanosis, and the

boot-shaped heart on x-ray are material aids in a proper diagnosis. Usually the cyanosis dates from birth and it is always present early in life.

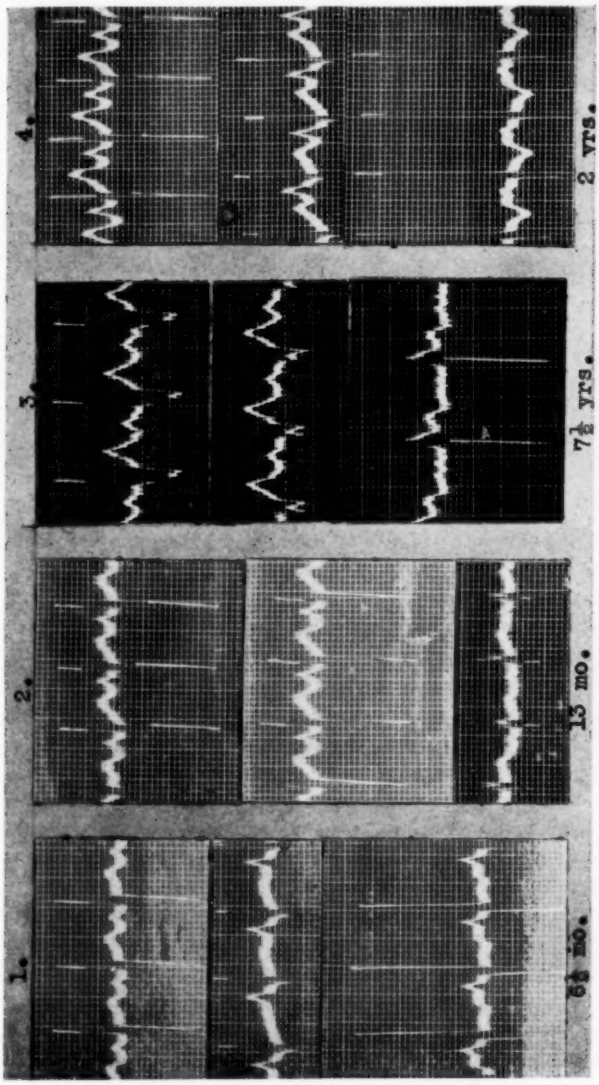

Fig. 5.—Suspected tetralogy of Fallot.

Case Reports of Suspected Tetralogy of Fallot (Fig. 5):

Case 1.—C. A. S., a girl, was born a blue baby, and was first seen at the age of 2 months. Nutrition was only fair at 17 months of age. Cyanosis was rather marked. The heart very slightly enlarged to percussion; there was a diffuse, not very loud

systolic murmur centered in mid-precordium. X-ray showed a heart of normal contour, possibly 10 to 15 per cent enlarged. An electrocardiogram (taken at 6 months of age) showed wide, diphasic QRS in Leads I and III, and rather high, pointed P-waves in Leads II and III.

CASE 2.—R. S., a boy, came to us because of blueness on crying since birth. At 13 months of age he weighed 15 pounds, and had a slight, definite cyanosis. The heart was not large to percussion. He had a moderately harsh systolic murmur maximum in the third left interspace. The x-ray showed a boot-shaped heart. Electrocardiogram (taken at 13 months of age) showed wide, diphasic QRS in Leads I and II, and no particular axis deviation.

CASE 3.—C. C., first seen at the age of 8 years, gave a history of cyanosis since birth. He had an intense cyanosis of the fingers and lips, and the fingers were clubbed. There was moderate dyspnea on exertion. The heart was not enlarged to percussion. A harsh, precordial systolic murmur was present, and x-ray showed a boot-shaped heart. The electrocardiogram showed a possible bundle branch block (?), a tendency to left axis deviation, and a widely diphasic QRS in Lead I.

CASE 4.—R. B., a boy aged 2½ years, was seen first at 8 months of age, because of his heart. There was a history of cyanosis from birth, and he had difficulty in lying down with comfort. He showed delayed development and was subject to attacks of convulsions. His heart was not enlarged to percussion; he had a short sharp systolic murmur in about mid-precordium. X-ray showed a typical boot-shaped heart. The electrocardiogram showed diphasic QRS in Leads I and III, right axis deviation, and pointed P waves in Leads I and II.

Comment.—There are likely to be significant changes in the electrocardiogram of every child with a congenital heart condition causing cyanosis, but these changes are not any more pathognomonic than the constant occurrence of high red blood cell counts in patients with congenital heart disease accompanied by cyanosis. However, these changes are just as characteristic as the high red cell count.

Ashman[11] writes that high, bizarre complexes suggest a congenital heart condition. Wachtel and Katz[5] state that widely diphasic QRS complexes may be considered pathognomonic of congenital heart disease. We should like to call attention to the fact that in our experience these variations from normal in the QRS complexes occur in the cyanotic congenital heart conditions fairly regularly and only seldom in the noncyanotic group. We also consider the high, pointed P waves in one or more leads found in the tracings of these severe, cyanotic congenital heart conditions of similar significance to the bizarre QRS complexes. These findings are readily discernible in Fig. 5.

Right axis deviation is generally found in tracings of tetralogy of Fallot, but a left axis deviation is not incompatible with the condition. A left axis deviation in a cyanotic child, however, calls for a careful survey of the possibilities.

TRANSPOSITION OF THE GREAT VESSELS AND CONGENITAL TRICUSPID ATRESIA

Definite progress has been made in recent years in differentiating clinically various congenital cardiac conditions causing cyanosis.[12]

Transposition of the vessels is the congenital cardiac condition in which the aorta comes from the right ventricle and the pulmonary artery from the left ventricle. In general, this congenital lesion should be kept in mind as a possibility when one sees a cyanotic child who has much respiratory distress and delayed physical development. Gibson and Clifton[13] noted that the outlook for life in transposition of the vessels is poor and that all patients with the condition who came to autopsy died before the age of about 2 years.

Taussig stated that all her cases of transposition of the vessels showed cardiac enlargement, especially of the right ventricle, a narrow aortic shadow in the anteroposterior roentgenogram, and an increase over normal in the width of the roentgenographic shadow cast by the great vessels in the left anterior oblique position on fluoroscopy.

Congenital tricuspid atresia occurs when the right ventricle is rudimentary. This nonfunctioning right ventricle is associated with atresia or hypoplasia of the tricuspid valve, an interauricular septal defect, and a severe malformation of the pulmonary artery. Taussig points out that the rudimentary right ventricle and the atresia of the pulmonary artery gives rise to a concave left border of the heart shadow where normally there is usually a convex border made by the pulmonic cone. This x-ray picture of a boot-shaped heart, associated with an electrocardiogram showing a definite left axis deviation, should make one consider the diagnosis of congenital tricuspid atresia.

Case Reports (Fig. 6):

CASE 1: *Transposition of the vessels* (Autopsied, not diagnosed correctly during life).—G. W. was first seen in the clinic when 7 months old, and died at 8½ months from bronchopneumonia. He was cyanotic from birth and developed slowly. The heart was slightly enlarged to percussion. There was a harsh precordial systolic murmur and definite thrill. The x-ray showed a heart shaped generally like a water flask with a wide neck. The electrocardiogram showed left axis deviation and a low diphasic QRS in Lead I.

At autopsy the heart showed hypertrophy of left side; two superior venae cavae; complete transposition of aorta and pulmonary arteries; bicuspid pulmonary valves; interventricular septal defect about 15 mm. in diameter; patent foramen ovale about 10 mm. in diameter.

CASE 2: *Congenital tricuspid atresia* (Autopsied, not diagnosed correctly during life).—D. W. died at the age of 3½ months. He had rapid respirations and intermittent cyanosis from birth. Nutrition of the child was poor. The heart was very large to percussion. There was a short, harsh systolic murmur, maximum at

the apex. X-ray did not show the concave border in the region of the pulmonic cone which Dr. Taussig says is characteristic. The electrocardiogram showed pointed, high P-waves in Leads I, II, and III, left axis deviation, and a diphasic QRS complex in Lead III.

Autopsy.—Atresia of tricuspid valve. Absence of the right ventricle. Transposition of the great vessels. Patent foramen ovale.

CASE 3: *Suspected congenital tricuspid atresia.*—M. P., a boy aged 5 years, with a history of blueness since birth, was malnourished and did not walk until the age of 3 years. He had marked cyanosis of features. The heart was slightly enlarged to percussion, with a marked systolic thrill and a harsh systolic murmur centering in mid-precordium. The x-ray showed the heart enlarged about 40 per cent, predominately of left side. There was a concave border at the left upper portion of the heart shadow where the pulmonic cone should have been. The electrocardiogram showed left axis deviation, a diphasic QRS in Lead I, and pointed, high P waves in Leads I and II.

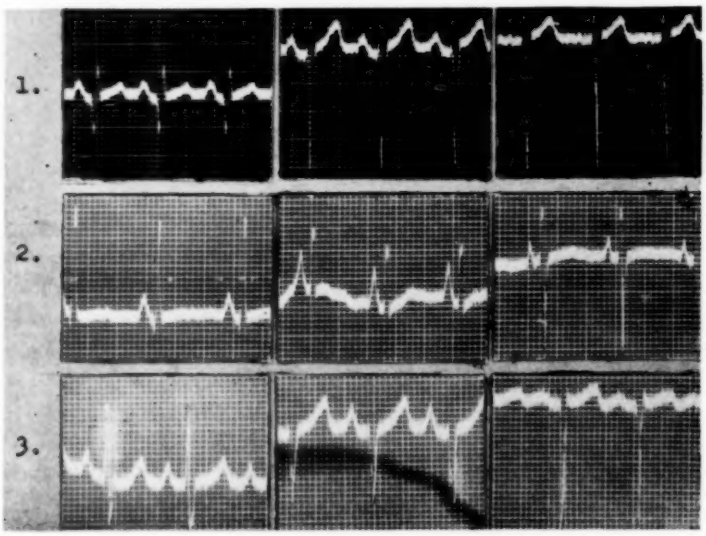

Fig. 6.—*1*, Electrocardiogram of patient with transposition of vessels (autopsied); death at age of 8½ months. *2*, Tricuspid atresia (autopsied); death at age of 3½ months. *3*, Suspected tricuspid atresia; age of patient, 5 years.

Comment.—In the cyanotic child, right axis deviation is the rule. In Schnitker's cases of tetralogy of Fallot, eleven of thirteen showed definite right axis deviation. When left axis deviation is present in a child with cyanosis, however, no specific diagnosis is possible on this finding alone. Schnitker has in his group of cases a common arterial trunk which gave rise to left axis deviation. We have an autopsied instance of transposition of the vessels with left axis deviation (Fig. 6, Case 1)

DEXTROCARDIA

When complete inversion of the viscera exists, the heart is in the right mediastinal area. Because of the absence of murmurs, and because the heart tones may be heard in the left chest area without difficulty, it is possible to overlook dextrocardia.

Isolated dextrocardia of congenital origin, a condition in which the heart, but not other viscera, is in dextroposition, in our experience has always been of a severe nature. These children have marked cyanosis, murmurs, and symptoms of cardiac distress, such as fatigue and dyspnea. Although isolated dextrocardia without symptoms is said to be twice as common, we have not encountered such instances.

Dextroposition of the heart may occur, for example, from atelectasis of the right lung lobes, which pulls the heart into the right chest, or from an effusion in the left pleural cavity which pushes the heart into the right chest. But such conditions seldom, if ever, are confused with the diagnosis of congenital dextrocardias.

Case Reports (Fig. 7):

CASE 1: *Complete inversion of the viscera.*—L. M. S., a girl, first known to us at the age of 6 months, was recognized as having a situs inversus. The x-ray showed the liver on the left side and the stomach on the right. In the electrocardiogram all the summits of the waves in Lead I were inverted and Leads II and III were transposed.

CASE 2: *Isolated dextrocardia.*—R. M., a boy, was thought to be normal at birth, but when 1 month old a mild degree of cyanosis was noted about the lips. The apex beat was palpable in the right chest, and there was a loud, coarse murmur at the base of the heart. The child developed very poorly and his cyanosis increased. Clubbing of fingers became prominent. At the age of 2 years he weighed only 21 pounds and did not walk or talk. X-ray showed a heart in the right chest area. It also showed a left lower lobe atelectasis. Bronchoscopic examination gave no clue as to the cause of the atelectasis. An electrocardiogram taken at the age of 5 months shows the first lead with inverted summits, as does the electrocardiogram taken at the age of about 2 years.

CASE 3: *Dextroposition of the heart due to atelectasis in right chest.*—R. H., a boy, was 6 months old at the time of examination. At 2 months of age, it was noted that his heart tones were heard best to the right of the sternum. He was never cyanotic. An x-ray revealed a right upper lobe atelectasis, with the heart to the right. In the electrocardiogram the P wave in Lead I was diphasic.

CASE 4: *Dextroposition of the heart due to an effusion in the left chest.*—W. J., aged 10 years, had a tuberculous pleurisy which pushed his heart into the right chest. The x-ray showed complete blotting out of the left lung field, with marked displacement of the heart to the right. Nothing unusual appeared in the electrocardiogram.

Comment.—The typical electrocardiogram is pathognomonic of complete inversion of the viscera. This is where the summits of the P, QRS, and T waves in Lead I are inverted, and Leads II and III are interchanged. Even where there is only the isolated congenital dextro-

cardia, the electrocardiogram reveals a first lead with the summits of the waves inverted (Case 2). Where dextrocardia occurs with either the auricles or ventricles in proper relationship, then apparently the

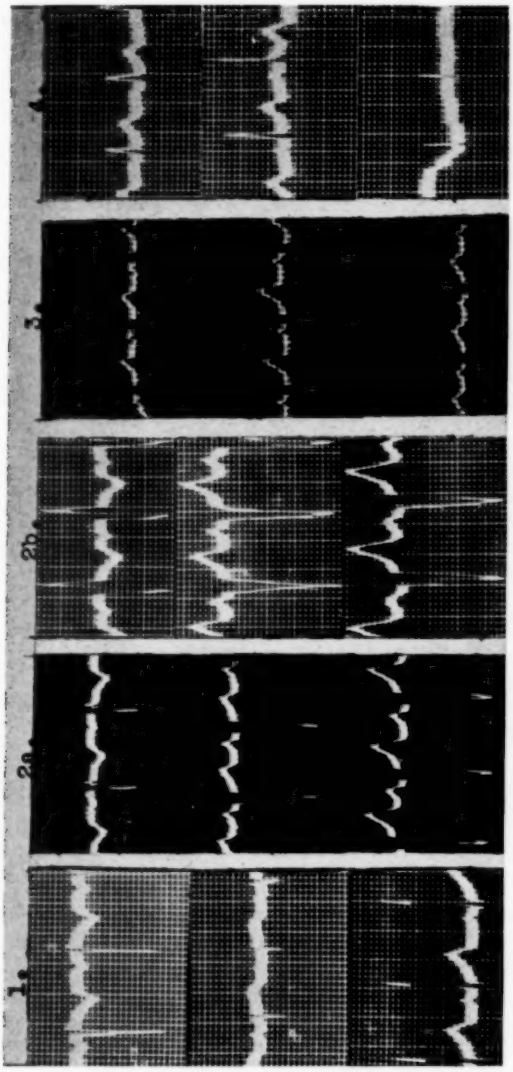

Fig. 7.—Dextrocardia. *1*, Complete inversion of viscera; age of patient, 10 months; *2*, Isolated dextrocardia: *a*, 5 months of age; *b*, 2 years. *3*, Dextroposition of heart due to right upper lobe atelectasis; age of patient, 6 months. *4*, Dextroposition of heart from pleural effusion; age of patient, 10 years.

electrocardiographic tracings do not give this easy clue. Thus, either the P wave or the QRS complex may be upright, depending on the position of the auricles and ventricles. We have not yet encountered this condition in our experience.

Mere position of the heart in the right chest is not enough to give the striking alteration in the leads that comes about with the congenital dextro-anomalies of the heart.

CONGENITAL HEART BLOCK

Congenital heart block can always be diagnosed by an electrocardiogram. The value of the tracing is infinitely greater if taken early in life. Before a diagnosis of congenital heart block can be made, it must be established that the child has a congenital heart condition. Yater and associates[14] state that there must be no influencing factor in the history to suggest another cause of heart block, particularly diphtheria or rheumatic fever.

While usually the pulse is slow in heart block, it may reach 60 to 80. For this reason, it is possible to overlook a heart block if electrocardiograms are not taken routinely on children with congenital heart disease.

The opinion is prevalent, and seems correct, that the block does not give rise to symptoms, and that such findings as are present, as malnutrition and clubbing of fingers, are due to the congenital heart condition.

Studies, particularly by Yater and his co-workers,[14] indicate that congenital heart block is usually due to a true anatomic defect in the bundle of His. There is generally a separation or interruption of the bundle from its A-V node. There must be also all degrees of anatomic breaks in the bundle of His to give rise to heart blocks of varying degrees and for varying periods. This probably accounts for the temporary complete heart block present in one of our patients (Case 3). In our cases, as in Schnitker's, block usually occurred in the children whose congenital heart conditions were serious and accompanied by cyanosis.

Case Reports (Fig. 8):

CASE 1: *Partial heart block.*—N. W., a colored girl aged 14 years, had the typical murmur of a patent ductus arteriosus. She was not cyanotic, was in a good state of nutrition, and attended regular school. She had no history of diphtheria or rheumatic fever. The x-ray showed a heart of normal size and contour. The electrocardiogram had one distinctive feature, a P-R interval of 0.26 second.

CASE 2: *Complete heart block.*—H. F., a boy, died at 20 months of age. (No autopsy was obtained.) A history was given of difficult resuscitation at birth and progressively increasing cyanosis since birth. His mother also said that at night "he breathed sometimes as if he was going to die." The patient was brought to us at 15 months of age. Noticeable were his marked cyanosis and poor nutrition. Heart dullness was as much to the right as to the left of the sternum. Systolic thrill and long blowing systolic murmur were maximum over the precordium. Heart rate was 50. The x-ray examination showed the heart 20 per cent enlarged. The apex of the heart was to the right. The electrocardiogram showed complete heart block, with a mirror image first lead.

CASE 3: *Temporary complete heart block.*—W. L., a boy aged 12 years, had bilateral colobomas of the irises, besides a congenital heart condition. He was

cyanotic, tired easily, and had clubbed fingers. He had a murmur suggesting a patent ductus arteriosus, and x-ray showed the boot-shaped heart of the tetralogy of Fallot. One electrocardiographic tracing showed a complete block; a tracing taken about six months later did not give evidence of the block.

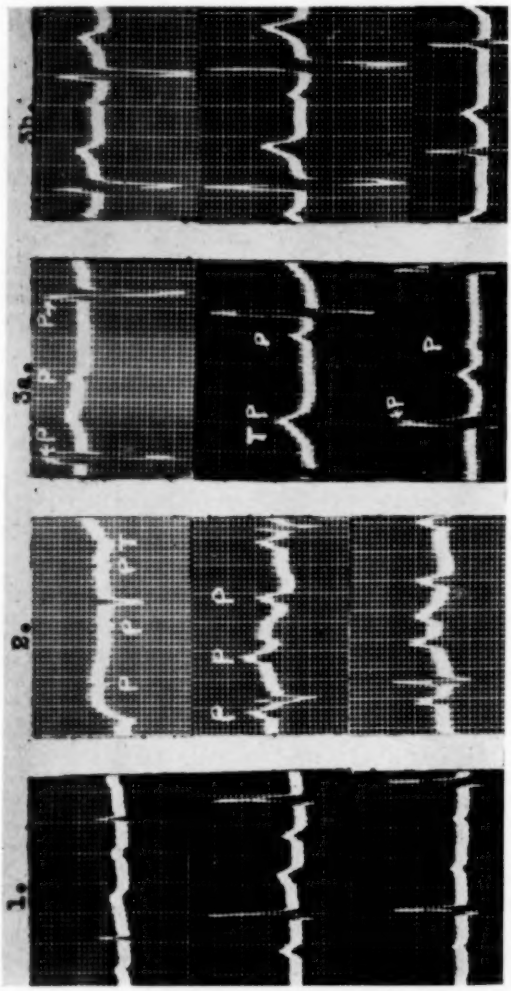

Fig. 8.—Congenital heart block. *1*, Partial block; patent ductus arteriosus; age of patient, 14 years; P-R interval, 0.26 sec. *2*, Complete block; age of patient, 15 months; note mirror image of first leads; auricular rate, 150; ventricular rate, 50. *3*, Temporary complete block: *a*, age of patient, 12 years; auricular rate, 100; ventricular rate, 50; *b*, age, 12½ years; P-R interval, 0.18 sec.

Comment.—Our experience with block would indicate that it is not connected with any one kind of congenital lesion, and that it is usually associated with more severe forms of congenital heart disease than uncomplicated interventricular septal defects. Generally when present, heart block is a constant permanent finding, but apparently it may be temporary (Fig. 8, Case 3).

There is nothing in the electrocardiographic tracing to distinguish congenital heart block from heart block due to other causes.

On several occasions, heart block was discovered with the taking of tracings routinely. We suggest that every child with congenital heart disease have occasional tracings taken, so that this condition is not overlooked.

SUMMARY

The electrocardiogram is a valuable aid in the study of congenital heart conditions. It will specifically reveal heart blocks and congenital dextrocardias which may be overlooked clinically. It is helpful in the differential diagnosis of cyanotic congenital heart conditions. It can give another reassuring bit of evidence in such cases of patent ductus arteriosus as are considered for surgery.

The more severe the congenital heart condition is, the more likely one is to find changes from normal in the electrocardiogram. The non-cyanotic group of congenital heart conditions seldom reveals changes; the cyanotic group usually does. The most characteristic changes to be found are bizarre, widely diphasic QRS complexes, and sharply pointed, high P waves in one or more leads.

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A CLINICAL STUDY CONCERNING THE VALUE OF BIOLAC

I. As a Suitable Food Substance
II. As a Source of Available Iron for Infants

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I. BIOLAC* AS A SUITABLE FOOD SUBSTANCE

PURPOSE

THIS study was designed to determine the value of biolac as a satisfactory source of food in artificially fed infants. The criteria employed in reaching a decision were increase in weight, increase in sitting height, increase in length, increase in head and chest circumference, development of motor and mental activity, dentition, and regularity and character of stools in a group of infants fed with biolac as compared with a control group of infants fed with modified pasteurized grade A milk.

PROCEDURE

Fifty normal infants were selected for this study. Since it was impossible to obtain fifty infants of appropriate ages at the same moment, it became necessary to place babies on the study as they became available. Each infant was observed for a period of five consecutive months. The total period of time required for this study was approximately one year.

The infants selected for this observation were divided into two groups of twenty-five each. Group A consisted of twenty-five infants who received formulas of pasteurized grade A milk, and Group B consisted of twenty-five infants who received formulas prepared with biolac. As far as possible, the distribution of age, sex, and race were the same in each group. The ages of the individual babies at the beginning of the study varied from 1 week to 6 weeks.

This study was executed under the supervision of the Council for Pediatric Research of the American Academy of Pediatrics. All expenses were defrayed by a grant from the Borden Company.

*Biolac is manufactured by the Borden Company. Its approximate composition is:

	UNDILUTED	DILUTED WITH EQUAL VOLUME OF WATER
Milk fat	4.8%	2.4%
Lactose	16.3%	8.2%
Protein	5.6%	2.8%
Mineral ash	1.3%	.6%
Water	72.0%	86.0%
Available iron		7 to 9 mg. per qt.
Calories per fluid ounce	38	19

Each tin (16 fluid oz.) contains not less than 2,000 I. U. vitamin A, 320 U.S.P. units vitamin D, and 80 I. U. vitamin B_1.

Since so many kinds of canned milk are commercially available, and since "standards" for the grade of milk employed for condensing or evaporating milk have not been established and show such wide variations, it should be stated that the milk employed in the preparation of biolac is inspected and approved by the health department in each locality in which biolac is prepared.

There were fourteen male infants and eleven female infants in Group A, and fifteen male infants and ten female infants in Group B (Table I). The subjects included in this study were of the white race, the Irish nationality predominating.

TABLE I

SEX AND AGE OF INFANTS AT BEGINNING OF STUDY

GROUP	AGE (WK.)	NO.	MALE	FEMALE
A (Grade A milk)	2	4	3	1
	3	6	4	2
	4	10	5	5
	5	4	1	3
	6	1	1	0
Total		25	14	11
B (Biolac)	1	1	1	0
	2	5	3	2
	3	10	6	4
	4	5	3	2
	5	4	2	2
Total		25	15	10

The infants were secured through the cooperation of the Brookline Friendly Society of Brookline, Mass., at whose clinic they were regular attendants. Each baby received a complete physical examination at the clinic prior to being accepted for the study. Every four weeks thereafter, each baby was returned to this clinic for physical examination, measurements, and observation by the physician and nurse. Data collected at the time of this examination were measurement of the circumference of the head and chest, total length, sitting height, and weight. At the time of this visit, dentition, muscular development, and mental activity of the baby were also noted.

NURSING SUPERVISION

As a precaution against errors in the preparation of the formulas and also as a means of determining whether or not the instructions and advice given to the parents at the time of their visit to the clinic were being followed, the home of each infant was visited once weekly, or, when indicated, twice weekly. These house visits were made by Miss M. G. Henderson, R.N., whose duties were confined to the supervision of the care of all infants from birth to 2 years of age. During these visits, Miss Henderson made comprehensive notes regarding the diet, incidence of infection, management of the baby, and its development.

Motor sequence and behavior manifestations of the baby were recorded during each visit in the home and at the time of the monthly physical examination at the clinic. These data were transcribed onto charts prepared by Dr. Mary Shirley, of the Department of Child Hygiene, Harvard School of Public Health.

Each mother kept a diary in which she made a daily record of the amount of formula ingested by the infant and the number and character of the stools. These diaries were reviewed at the times of the nurse's visits to the home and also at the times of the visits to the clinic.

FORMULAS

The formula in Group A consisted of whole milk, corn syrup, and water. The antirachitic factor was furnished in the form of White's cod-liver oil concentrate, 8 drops daily, and the antiscorbutic factor, in the form of cevitamic acid tablets, 25 mg. daily. The formula in Group B consisted of biolac, which was supplied in 16 oz. tins. Each tin contained added lactose as a carbohydrate and cod-liver oil concentrate to the amount of not less than 320 U.S.P. vitamin D units per quart after dilution, equivalent to the A. M. A. prophylactic level. The antiscorbutic factor was supplied in the form of cevitamic acid tablets, 25 mg. daily.

The composition of the formulas was altered during the presence of infections or when it became necessary to increase the caloric content of the diet. At appropriate stages in the development of the infants, stewed fruits, cereal, vegetables, and meat were added to the diet. It is likely, therefore, that the diet of each infant supplied all the recognized nutritional requirements.

RESULTS*

Circumference of the Head.—The circumference of the head of each infant was measured at monthly intervals, and it was noted that although there were some differences in the monthly measurements of the two groups, yet there was no significant difference in the total increment at the end of the study between Group A infants and Group B infants.

Circumference of the Chest.—In the same manner, the circumference of the chest of each infant was measured periodically. There was no significant difference in the increase in chest circumference of the two groups of infants as determined by the total increment at the end of the study.

Sitting Height and Total Length.—Monthly measurements of the sitting height and total length of the two groups of infants showed individual monthly variations in the two groups, but, as with the other measurements, there was no significant difference between Group A infants and Group B infants at the end of the period of observation.

Weight Increase.—The weight in pounds and ounces of each infant at the beginning of the study and at each subsequent examination was recorded, and it was noted that the gain in weight, in total increment,

*All of the measurements on each infant studied have been included in the numerous tables in the report submitted to the Council for Pediatric Research. For the sake of brevity, however, these tables have been omitted from the present presentation, and the summary of the various measurements is reported briefly here.

was greater in Group A males than in Group B males. There was no significant difference in the gain in weight between Group A females and Group B females.

Activity and Dentition.—An examination of the recorded data fails to reveal any significant difference in the motor or mental development of the two groups, as both groups of infants advanced at about the same rate. A similar statement can be made in regard to dentition.

Stools.—The average number of daily stools in Group A females, was 2.18, as compared with 2.60 in Group B females. Group A males had an average daily number of stools of 2.40, as compared with 2.10 in Group B males. However, the character of the stools of the two groups did show some difference in so far as the stools of the babies fed with biolac (Group B) were of a softer character, were more easily expelled by the infant, and simulated those seen in breast-fed infants.

TABLE II

INFECTIONS IN GROUP A

	Males
D. C.	Two mild respiratory infections
J. D.	One mild respiratory infection
A. H.	One mild respiratory infection; nonspecific conjunctivitis
T. K.	Two mild respiratory infections
R. L.	"Intestinal grippe"
E. L.	One mild respiratory infection
F. L.	One mild respiratory infection
L. McN.	One mild respiratory infection; chickenpox
	Females
P. D.	Two mild respiratory infections
P. D.	One upper respiratory infection; arrested hydrocephalus
N. E.	One upper respiratory infection
E. H.	Three upper respiratory infections
B. P.	Eczema; two upper respiratory infections
S. Z.	One upper respiratory infection; bronchitis

TABLE III

INFECTIONS IN GROUP B

	Males
J. M.	One mild respiratory infection
A. F.	Otitis media, suppurative; impetigo
R. F.	One mild upper respiratory infection
R. N.	One mild upper respiratory infection
	Females
M. C.	One mild respiratory infection
C. K.	One mild respiratory infection
J. O'C.	Conjunctivitis and tonsillitis at the time of admission to the study
H. O.	Conjunctivitis at time of admission to the study

Infections.—The incidence of infection occurring among the two groups (Tables II and III) showed a higher rate among Group A infants than among Group B infants. This difference was rather pro-

nounced. Group A males had twelve infectious among eight infants, as compared with five infections among four Group B males. Group A females had eleven infections among six infants as compared with two infections among two female infants in Group B. Two Group B females had mild infections at the time of their admission to the study and therefore are not included in these figures; they do appear in Table III.

DISCUSSION

Roentgen-ray studies to determine the possible development of rickets among these fifty artificially fed babies were not made. However, at no time was there any clinical evidence to suggest the presence of this deficiency disease. Thus, one may reasonably conclude that the vitamin D intake of each infant was adequate, regardless of whether the vitamin was incorporated in the formula (biolac) or whether it was given separately in the form of a concentrate. Nor were there any clinical signs or symptoms to suggest a vitamin C deficiency.

There is no apparent explanation for the difference in the incidence of infections in Groups A and B. One would hesitate to assume that any dietary difference was responsible.

No difficulties were encountered in getting the babies to take the biolac formula. Thus, it would appear that the addition of cod-liver oil concentrate to the preparation did not give it in any manner an objectionable taste.

It has been previously stated in this report that there was little if any difference in the average daily number of stools of the two groups. However, it should be mentioned that periods of soft stools unrelated to infections did occur more frequently among the babies fed biolac than among the babies fed with pasteurized grade A milk. These difficulties were not encountered during the fall or winter months, appearing only when the weather was humid or very hot.

A study of the tables presented in this report would at first give the impression that the babies who received formulas prepared from pasteurized grade A milk showed a more rapid rate of growth than did those babies who received formulas prepared from biolac. This impression is due to the fact that the majority of the babies comprising Group B were smaller than those comprising Group A. That such a difference should occur is unfortunate and was purely accidental, as such discrimination was not employed. In fact, the babies were placed in either Group A or Group B in an alternate manner. In an effort to exclude this difference in the final appraisal of the study, all measurements have been submitted to Dr. Carl R. Doering, of the Department of Vital Statistics, Harvard School of Public Health, Harvard Medical School, for his examination. Dr. Doering's report is here quoted, in part:

"If the increments of growth for the various measurements between successive age periods are taken and those for Group A and B are com-

pared, it is found that there is no statistically significant difference between them. This comparison ignores the difference between the groups at any given age for any given growth factor and deals only with the gains shown between examinations.

"The general conclusion may be drawn that although the sample showed the A group to be greater than the B group at the very beginning and also throughout the experiment, the gains made from month to month by the two groups were practically the same."

II. THE AVAILABILITY OF AND THE RESPONSE TO THE IRON CONTAINED IN BIOLAC

After it had been determined that biolac serves as a satisfactory food in artificially fed infants, it was necessary to evaluate clinically the response to the iron contained in this prepared food.

Before the eighth to tenth week of life, there is ordinarily little evidence of iron deficiency, and iron is not necessary, either as a prophylactic or as a therapeutic measure. In fact, the administration of iron before this time may produce little or no demonstrable effect on the blood of the individual. After the tenth week of life, depending upon the health and blood levels of the mother during gestation and the amount of iron stored by the fetus before birth, there may be more or less need for iron, and in the poorly endowed child of an anemic mother, iron deficiency may begin to be manifest. At this time iron medication or iron in the food may produce a demonstrable improvement. Usually, after the twentieth week, infants are offered soft-solid foods, some of which contain iron in appreciable amounts. Changes in the blood may be noted then because of the iron content of these foods. For the purpose of this study, infants in apparent good health, free of infection or nutritional disturbance, and between the ages of 8 and 16 weeks were selected.

METHOD OF PROCEDURE

Groups of infants, numbering from four to six individuals aged between 8 to 16 weeks, were selected. Such small groups could be followed at frequent intervals without difficulty as regarded measurements of their blood cell and hemoglobin values. All of these infants had previously been fed on only a whole milk-karo-water modification with the addition of vitamin C in the form of ascorbic acid tablets and vitamins A and D in natural oil concentrate. Since the infants were admitted to the nursery shortly after birth, sufficient time had elapsed to exclude from the study those with acquired or congenital disease or with congenital malformation or disturbances interfering with their normal growth and development. In general, the economic level of the mother was low, and, therefore, many of these infants had poor stores of iron as evidenced by the development of an iron-deficiency anemia in the third month of life if uncorrected by food or medicinal means. Any

evidence of acute infection or nutritional disturbance, such as vomiting, diarrhea, or failure to gain in weight, was grounds for excluding the individual from the study group. Because of this latter condition, twenty-eight infants were begun on this study during the course of a year, and only twenty complete records were acceptable at the end of this time.

Careful notes were kept to insure accurate knowledge as to the patient's gain in weight, freedom from vomiting and diarrhea, or evidences of infection. In addition to the biolac, only vitamin C in the form of ascorbic acid tablets, 25 mg. daily, was given to each patient. The medicinal iron was an elixir of ferrous sulfate, given in the amounts indicated at the time noted.

Each infant was subjected to the following hematologic measurements which were made three times a week: Blood was obtained from a needle puncture wound in the heel of sufficient depth to allow a free flow of droplets of blood. The erythrocyte estimation was made by the usual method, using certified blood pipettes and a certified counting chamber; percentage of hemoglobin was determined in a photoelectric cell colorimeter by the method of Evelyn, the value of 100 per cent being 15.6 Gm. per 100 c.c. of blood; percentage of reticulocytes was estimated from the counting of 2,000 erythrocytes in cover slip smears stained with cresyl blue and counterstained with Wright stain.

The period of study was divided into four parts. As a control period during a first period of fourteen to eighteen days, each patient was given biolac without iron. During the second interval of fourteen to eighteen days, the patient was given biolac containing iron in a level of between 7 and 9 mg. daily. During a third interval of fourteen to eighteen days, biolac without iron was once more administered, and as a source of mineral iron, 1 c.c. of the elixir of ferrous sulfate containing approximately 7 to 9 mg. of metallic iron were given. (This variation of 1 to 2 mg. in daily iron intake was insufficient to produce demonstrable biologic effect.) During the fourth period of fourteen to eighteen days, the patient was given biolac without iron and ferrous sulfate elixir in the amount of 4 c.c. per day, administered between meals, which offered about 26 mg. of metallic iron daily. This quadruple amount of previous iron administration served to emphasize the value of iron to the patient and the specificity of the blood response to this element.

RESULTS

In order to interpret the results obtained in these infants during the nine weeks of study, it was necessary to regroup them according to the individual age at the onset of the study period. As has been demonstrated repeatedly, a normal mild degree of hypochromic anemia may develop during the first ten to twelve weeks of life of the normal full-term infant. Thereafter normally there is a tendency for improvement of erythrocyte and hemoglobin levels so that a regular curve is followed

from birth through about the fifth month of life. Any comparisons, therefore, of the blood levels of different infants during this neonatal period should be made between individuals of approximately the same age only, in order to guard against an erroneous interpretation dependent upon the different physiologic levels present in each month during the first five months of life. For this reason, the twenty infants studied were redivided into three groups: Group I, consisting of seven individuals, were aged between 8 and 10 weeks at the onset of their study period; Group II, consisting of seven individuals, were aged between 11 and 13 weeks at the onset of the study period; Group III, consisting of six individuals, were aged between 14 and 16 weeks at the onset of this study period.

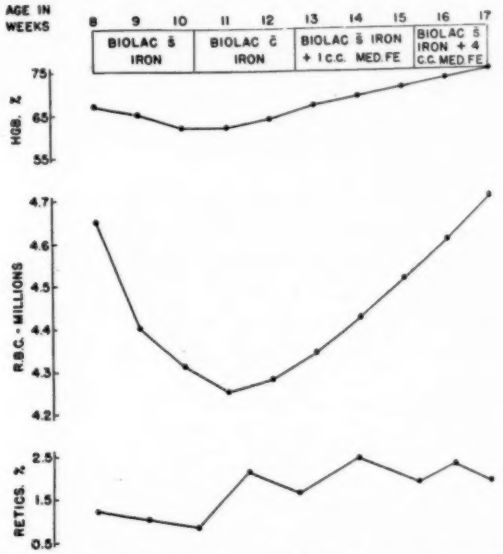

Fig. 1.—Group I. Seven infants aged 8, 9, and 10 weeks at onset of study.

The results are seen best in the graphic representation of the hemoglobin, erythrocyte, and reticulocyte levels of the infants in each group as shown in Figs. 1-3. For the sake of simplicity, the values were charted at weekly intervals, and each point is the average of all the individuals in the group. The differences between the various infants in each group as regards hemoglobin, erythrocyte, and reticulocyte levels were sufficiently small to permit of such an average being made. In Fig. 1 (Group I) it is seen that during period 1, when biolac without iron was given, there was a steady fall in erythrocyte and hemoglobin values and very few reticulocytes (less than 1 per cent) in the stained smears of the blood. In period 2, when biolac with iron was substituted, a reticulocyte response up to 2.1 per cent occurred at the end of about

one week, and subsequent to this there was a rise in erythrocyte and hemoglobin values. In period 3, when biolac without iron, but with an equivalent amount of iron in the form of ferrous sulfate, was given, there was further reticulocyte response up to 2.4 per cent and a further rise in erythrocyte and hemoglobin values. This may be interpreted as indicating that the medicinal iron even at the same level of daily intake was more effective in producing a response on the part of the blood and, therefore, gave better results. This was expected for two reasons. In the first place, the iron present in biolac is in the form of ferric ammonium citrate, which is less effective than ferrous sulfate, the medicinal iron offered. In the second place, it has been shown repeatedly that iron administered in a phosphate-containing vehicle, such as milk, is less effective because of the possible precipitation of insoluble iron phosphates. In period 4, biolac without iron and a quadruple amount of metallic iron were administered to each infant, and again there was a definite response in reticulocytes to 2.2 per cent and still further rise in the hemoglobin and erythrocyte levels, showing the specific effect of the iron medication on the infant suffering from a mild iron deficiency.

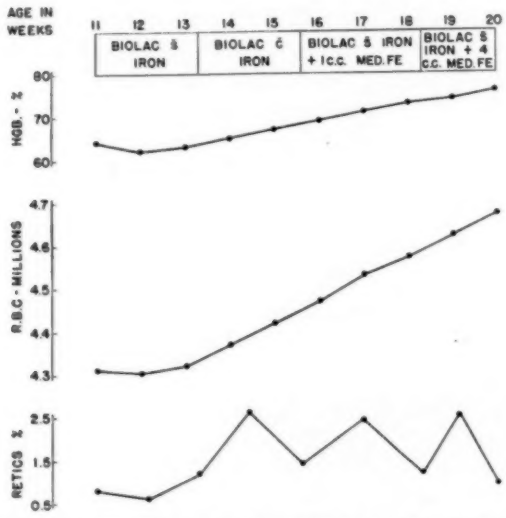

Fig. 2.—Group II. Seven infants aged 11, 12, and 13 weeks at onset of study.

In Fig. 2 (Group II) the same general results are seen. During the first period without iron, there was a slight fall in hemoglobin and erythrocyte levels and a few reticulocytes (less than 1 per cent) in peripheral blood smears. During the second period, when iron was present in the biolac, a reticulocyte response of 2.6 per cent was seen at the end of a week, and the erythrocyte and hemoglobin levels began to

rise. During the third period, when biolac without iron, but with an equivalent amount of ferrous sulfate, was given between meals, there was a further reticulocyte response up to 2.4 per cent and a further rise in hemoglobin and erythrocyte levels. During the fourth period, when the amount of medicinal iron was increased fourfold, there was still another reticulocytosis of 2 per cent at the end of a week and a continuation of the hemoglobin and erythrocyte improvement.

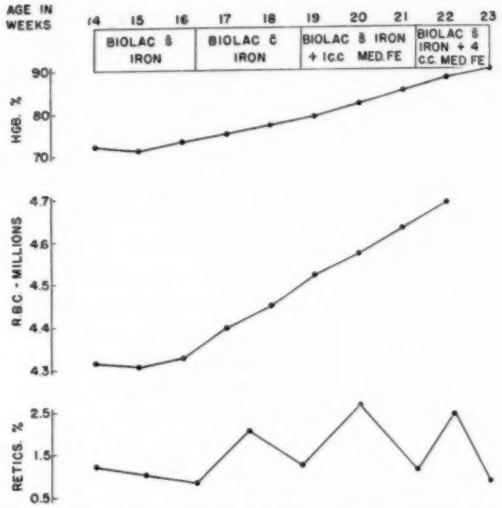

Fig. 3.—Group III. Six infants aged 14, 15, and 16 weeks at onset of study.

In Fig. 3 (Group III) during period 1, there was no demonstrable change in hemoglobin or erythrocyte levels, and the reticulocytes were 1 per cent or less. During period 2, when iron was present in the biolac, there was a reticulocytosis of about 2.1 per cent at the end of a week and a rise in erythrocyte and hemoglobin levels. During period 3, when medicinal iron was given between feedings in place of the iron in biolac, there was further reticulocyte response up to 2.6 per cent and a further increase in erythrocyte and hemoglobin values. During period 4, when the medicinal iron between meals was increased four times, there was still a third reticulocytosis up to 2.4 per cent and a continuation of the erythrocyte and hemoglobin improvement.

DISCUSSION

Since 1927, when Minot and his associates showed that the specific response to liver extract or liver-containing material in the patient with pernicious anemia may be judged by the reticulocytosis that results in the individual, it has been accepted that this measurement is a more delicate and accurate index of specific response to blood-building mate-

rial than either the erythrocyte or hemoglobin evaluations. Not only does such reticulocytosis follow the administration of the erythrocyte maturating factor in the patients with pernicious anemia, but also it follows the administration of iron to the patient with any degree of iron deficiency. It has been used, therefore, as a biologic index in the presence of a specific form of anemia due to the administration of a specific substance and the availability of the substance to the patient receiving it. In this case, the measurement has been used as an evidence of iron absorption in infants with mild to moderate degrees of hypochromic anemia. From the chart it can be seen that when iron is administered in the level of 7 to 9 mg. per day in the form of biolac containing iron, there is a small but definite reticulocyte increase at the end of a week and a subsequent rise in erythrocyte and hemoglobin values. As might be expected, this rise is not as great as that which occurs with a more available form of iron, such as ferrous sulfate, and the administration of this available iron between meals rather than in a milk medium. However, the feeding of biolac with iron served as a satisfactory method of increasing the iron intake which was especially necessary for the infants in this study group and is of great value to many infants in this age period. It is of some advantage to have iron present in food rather than to administer it as a medication, especially if it can be so given in a palatable and at the same time effective form. Although a larger amount of iron might produce a better response, it is questionable whether such an effect should be sought by enriching further food relatively poor in iron.

CONCLUSIONS

Biolac may be used as a satisfactory and suitable food substance for infant feeding.

The iron content of biolac is adequate and available for the building of new red cells and for the improvement in erythrocyte and hemoglobin levels. This is an important factor for infants in that period of life when milk alone is the principal food.

CUTANEOUS REACTIONS WITH SPECIFIC SOLUBLE SUBSTANCE IN INFANTS AND CHILDREN

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ALONG with recent developments in the specific therapy of pneumonia, the search for more information concerning the immunologic mechanism has enhanced interest in cutaneous reactions to specific soluble substance in pneumococcus infections.

In 1929, Tillet and Francis[1] showed that when polysaccharides derived from pneumococcus cultures were injected intradermally into patients convalescing from pneumonia, a wheal and erythema appeared in ten to twenty minutes and disappeared in one to two hours. This occurred only with polysaccharide homologous in type with the pneumococcus causing the infection. Francis,[2] in 1933, suggested that this reaction could be used as a guide for serum therapy. After each dose of serum, 0.1 c.c. of polysaccharide is injected, and when a positive reaction occurs, serum is discontinued. The studies published by Wood[3, 4] in January, 1940, offered more evidence that the Francis test is a reliable guide for serum therapy as well as a valuable prognostic aid. Relatively little has been done, however, to verify these reactions in infants and children.

Forty-two cases of typed pneumococcus pneumonia in infants and children were studied with pneumococcus capsular carbohydrate. The use of this material as a guide for serum therapy is known as the Francis test, and this test has been accepted generally as an index of the proper dose of antipneumococcic serum in the pneumonias of adults. Its value for controlling the dose of serum in infants and children was confirmed in the cases we studied. However, in our experience the results of the test following chemotherapy with sulfapyridine or sulfathiazole have been irregular and unpredictable.

Improved methods of pneumococcus typing offered an opportunity for studying these reactions in infants and children. A 1:1,000 dilution of pneumococcic carbohydrate substance was injected intradermally in 0.1 c.c. amounts. Where positive reactions were obtained, they corresponded to those described in adult patients. A wheal surrounded by a zone of erythema appeared in ten to twenty minutes and disappeared in one to two hours. In the stronger reactions the wheal gradually became deeper, disappearing from the epidermis into the deeper skin layers, often persisting there for twenty-four to forty-eight hours. It is the im-

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The specific carbohydrate substance was furnished by the Lederle Laboratories, Inc., Pearl River, N. Y.; the specific antipneumococcus serum was furnished for "clinical trial" by the Lederle Laboratories, Inc.

mediate erythema and wheal, however, that constitute the typical immune reaction and may disappear completely in one to two hours.

An attempt was made to verify the concept that the reaction is due to a local union of antigen and antibody. A normal infant received 0.1 c.c. of specific soluble substance intradermally in one area and twelve hours later in another. Neither injection produced a reaction. One hour after the second inoculation, both areas, as well as a third, received 0.05 c.c. of homologous serum. The sites that had received specific soluble substance showed strong wheal and erythema reactions, the older being much more diffuse. The control was entirely negative. Three other normal children duplicated these reactions.

Forty-two cases of typed pneumococcus pneumonia were studied. The distribution according to therapy was: sulfapyridine and serum, nine; sulfathiazole and serum, twelve; sulfapyridine, nine; sulfathiazole, twelve.

SERUM AND DRUG

When patients treated with both serum and drug were first studied, no attempt was made to control the dose of serum by the Francis test. After the usual testing for serum sensitivity was completed, an initial intravenous dose of 0.5 c.c. for patients less than 2 years of age and 1 c.c. for older children was given. One hour later another dose, usually 5 to 10 c.c., was administered intravenously, and sometimes a third dose an hour after the second. One-half hour before each dose, 0.1 c.c. of specific soluble substance was injected intradermally.

All but two of this group showed strongly positive reactions after the second dose, and positive reactions were obtained in these two patients after the third dose. All these patients maintained strongly positive reactions throughout the rest of their hospital stay.

When serum-treated patients were first studied, it was noted that when the Francis test became positive, areas that had been previously injected with specific soluble substance with negative results showed typical erythema and wheal reactions after the last dose of serum. Therefore, in the latter half of this series, only one skin test was administered before any serum was given, and this area was observed after each dose of serum. Typical reactions, when they occurred, were usually seen five to fifteen minutes after serum was administered.

In the early part of the study, serum reactions, consisting of marked temperature elevations and chills, were occasionally encountered when single intravenous doses larger than 5 c.c. were given. Following this observation, single doses were limited to 5 c.c. and fewer reactions occurred. Furthermore, in these later cases, when the Francis test became positive, serum was discontinued. Much smaller amounts of serum then were used with apparently comparable therapeutic effect.

In only one case did the temperature again become elevated after the Francis test was positive and serum was discontinued. This patient was critically ill and received 84,000 units of type VII serum. The skin test became positive, and the temperature fell to normal. The next day, however, the temperature was elevated, and the Francis test was negative. After an additional 70,000 units of serum were given, the skin test became positive and the patient became afebrile.

CHEMOTHERAPY ONLY

The nine patients who received sulfapyridine only and the twelve who received sulfathiazole only were followed with daily skin tests during the first four or five days after admission and subsequently every other day during the remainder of their hospital stay.

TABLE I

NAME	DAY PNEUMONIA REACTION BECAME POSITIVE	DAY POSITIVE REACTION BECAME NEGATIVE	HEIGHT OF REACTION
Sulfapyridine Cases			
E. A.	11	*	Strong
M. B.	0	0	0
P. B.	0	0	0
R. C. (1)	3	5	Weak
(2)	3	5	Weak
B. D.	0	0	0
M. J. M.	2	*	Moderate
J. S.	3	*	Moderate
R. S.	2	*	Moderate
J. W.	6	*	Strong
Sulfathiazole Cases			
W. B.	6	*	Strong
N. B.	4	*	Moderate
N. C.	0		0
A. D.	3	*	Strong
R. F.	0	0	0
A. G.	3	5	Moderate
M. G.	2	5	Moderate
K. K.	6	*	Moderate
R. L.	6	*	Strong
B. L.	6	*	Moderate
J. W.	5	7	Strong
D. W.	0	0	0

*Reaction still positive when discharged.

Three patients treated with sulfapyridine and three treated with sulfathiazole gave consistently negative reactions.

Five patients treated with sulfapyridine and nine treated with sulfathiazole first showed positive reactions on the second to the sixth day of the disease.

One patient treated with sulfapyridine first showed a positive reaction on the eleventh day.

In two patients treated with sulfapyridine and three treated with sulfathiazole, reactions were negative after two or three days of positive tests. In the remainder of the patients, the test was still positive when they were discharged from the hospital.

RECURRENT PNEUMONIA

Four patients with recurrent pneumonia were followed with skin tests. Two of these patients were treated during two admissions with sulfapyridine alone and at no time showed positive reactions. The third patient was a 9-month-old infant who received sulfapyridine for his first attack of type XIV pneumococcic pneumonia and had a prompt drop in temperature but was readmitted with a recurrence of the pneumonia one week after he was discharged from the hospital. The Francis test on admission was negative but became strongly positive after he received 31,500 units of type XIV antipneumococcic serum. At the time of discharge from the hospital one week later, skin reactions were still strongly positive. A 6-month-old infant was treated for three attacks of type XIV pneumococcus pneumonia with sulfapyridine, and the Francis test was consistently negative. He was given sulfathiazole and serum during his fourth attack. Before serum was given, specific soluble substance produced no reaction. After 16,500 units of type XIV antipneumococcic serum were given, the area where the skin test had been given showed a strongly positive reaction. The Francis test was repeated frequently during the following month and remained strongly positive.

SUMMARY

Forty-two patients with typed pneumococcus pneumonia were studied with the Francis test. Of these, nine were treated with sulfapyridine, twelve with sulfathiazole, nine with sulfapyridine and serum, and twelve with sulfathiazole and serum.

The positive reaction probably is due to a local union of antigen and antibody.

When specific antipneumococcic serum was given intravenously, it was found that only one skin test needed to be administered, and after this area became positive, serum therapy could be discontinued. The optimal dosage of serum is still in doubt. After single intravenous doses were limited to 5 c.c., fewer serum reactions, consisting of chills and temperature elevations, were encountered. By utilizing the Francis test, less serum was given with comparable therapeutic effect.

The time of development and intensity of cutaneous reactions varied greatly when patients received only chemotherapy. On the other hand, the patients who received serum developed strong reactions which persisted throughout their hospital stay.

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THE EFFECT OF HONEY UPON CALCIUM RETENTIONS IN INFANTS

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IN A recent publication[3] we have discussed the use of honey as a carbohydrate in infant feeding. On the basis of the general well-being of the infant, the number of stools per day, weight gains, and blood sugar tolerance studies, we concluded that honey would seem to be well suited to the infant's needs. In the present paper we wish to offer data in regard to the effect of honey upon calcium retentions.

Our report contains data from fourteen healthy male infants studied during the first six months of their lives. A total of 120 metabolism periods have been completed on these normal infants. Honey as a source of carbohydrate was compared with corn syrup for different types of milks and for varying levels of vitamin D. For fifty-nine of the metabolism periods the infants were fed formulas containing evaporated milk either with or without lactic acid. During fifty periods dried half-skim milk was used, while for seven and four periods, respectively, the infants received breast milk and dried protein milk. Vitamin D was usually furnished in the form of cod-liver oil at varying levels, but during certain periods either solutions of a crystalline preparation or Drisdol was used. Additional vitamins and minerals were furnished by supplements of cevitamic acid, thiamin, carotene, ferric pyrophosphate, and copper sulfate.

During the metabolism periods, which were always of five days' duration each, the feedings were given to the infants without loss, and the bottles were rinsed with distilled water which was either consumed at once or added to the next feeding. A rest period of three days was allowed for adjustment between collection periods, unless an important change in formula had been made, in which case five to seven days were given to permit a return to equilibrium.

Urine and feces were quantitatively collected during the five-day metabolism periods. The urine was preserved by toluene and refrigeration, enough concentrated hydrochloric acid being added to make the urine acid to methyl red. Feces were marked off by carmine and preserved during the collection period by acid alcohol (5 per cent glacial acetic acid in 95 per cent alcohol) and refrigeration. The feces were prepared for analysis by drying to constant weight, at first on a steam

Assistance in the preparation of these materials was furnished by the personnel of Work Projects Administration Official Project No. 665-54-3-387.

The various milks were furnished through the courtesy of the Evaporated Milk Association, the Borden Company, and Mead Johnson & Company. Honey, carefully selected as to source, purity, and uniformity, was supplied by the Lake Shore Honey Company.

Table I

Average Daily Calcium Balances

Subject	Period	Age (wk.)	Wt. (kg.)	Formula*	Vitamin D (I.U.)	Calcium					Phosphorus	
						Intake (gm./day)	Urine (gm./day)	Feces (gm./day)	Retention (gm./day)	Retention (mg./kg.)	Intake (gm./day)	Feces (gm./day)
John	1	9	4.78	E. LA.-CS.	170	0.647	0.007	0.513	0.127	26.5	0.521	
	2	11	4.99	E. LA.-CS.	170	0.656	0.004	0.549	0.103	20.6	0.521	
	3	12	5.27	E. LA.-H.	170	0.731	0.008	0.532	0.192	36.5	0.575	
	4	13	5.42	E. LA.-H.	170	0.691	0.003	0.494	0.195	36.0	0.575	
	5	14	5.76	Evap.-H.	170	0.772	0.003	0.635	0.134	23.3	0.644	
	6	16	6.05	Evap.-H.	170	0.720	0.006	0.494	0.221	36.4	0.644	
	7	17	6.43	Evap.-H.	170	0.754	0.005	0.522	0.227	35.3	0.644	
	8	19	6.76	Evap.-H.	170	0.783	0.006	0.542	0.235	34.7	0.644	
	9	20	6.99	Evap.-H.	170	0.669	0.006	0.516	0.148	21.1	0.644	
	10	22	7.15	Evap.-H.	680	0.745	0.009	0.511	0.225	31.5	0.644	
Bart	1	6	4.13	Dry.-H.	1,000	0.824	0.001	0.539	0.284	68.7	0.610	
	2	7	4.43	Dry.-H.	1,000	0.942	0.004	0.626	0.312	70.5	0.696	
	3	12	5.27	Dry.-H.	170	1.177	0.005	0.830	0.342	65.2	0.870	
	4	14	5.48	Dry.-H.	170	1.177	0.005	0.808	0.365	66.6	0.870	
	5	15	5.82	Dry.-CS.	170	1.295	0.004	1.038	0.253	44.2	0.958	
	6	16	6.16	Dry.-CS.	170	1.412	0.006	1.030	0.377	62.9	1.044	
	7	18	6.35	Dry.-H.	170	1.412	0.012	1.176	0.224	35.7	1.044	
	8	19	6.39	Dry.-H.	170	1.412	0.012	1.025	0.375	58.5	1.044	
Hal	1	8	3.64	E. LA.-H.	0	0.602	0.008	0.420	0.174	45.3	0.470	
	2	9	3.90	E. LA.-H.	0	0.587	0.003	0.427	0.157	39.0	0.457	
	3	11	4.25	E. LA.-H.	0	0.642	0.004	0.478	0.161	37.8	0.500	
	4	12	4.52	E. LA.-H.	1,000	0.636	0.006	0.423	0.207	45.8	0.500	
	5	13	4.78	E. LA.-H.	1,000	0.640	0.004	0.411	0.225	47.2	0.500	
	6	15	5.04	E. LA.-H.	1,000	0.640	0.011	0.435	0.194	38.5	0.500	
	7	20	5.55	Dry.-H.	680	1.129	0.008	0.681	0.439	79.1	0.870	
	8	21	5.80	Dry.-H.	680	1.129	0.009	0.752	0.367	63.4	0.870	
	9	23	6.35	Dry.-H.	680	1.298	0.014	0.799	0.485	76.4	1.000	
	10	25	6.63	Dry.-H.	680	1.298	0.025	1.039	0.234	35.2	1.000	
	11	26	6.94	Dry.-H.	680	1.399	0.014	0.727	0.659	94.9	1.080	

Ned	2	9	3.99	Dry.-H.	170	1.099	0.025	0.978	0.097	24.4	0.782	0.229
	3	13	4.45	Dry.-H.	170	1.222	0.033	1.116	0.073	16.4	0.870	0.242
	4	16	4.82	Dry.-CS.	170	1.222	0.031	1.091	0.099	20.6	0.870	0.273
	5	17	5.10	Dry.-CS.	170	1.344	0.039	1.261	0.045	8.7	0.958	0.336
	6	19	5.44	Dry.-CS.	170	1.344	0.059	1.265	0.020	3.6	0.958	0.352
	7	20	4.68	Dry.-CS.	170	1.466	0.042	1.354	0.071	12.5	1.044	0.348
	8	21	5.88	Dry.-H.	170	1.466	0.055	1.175	0.236	40.2	1.044	0.315
	9	23	6.10	Dry.-H.	170	1.588	0.060	1.424	0.104	17.1	1.132	0.395
	10	24	6.36	Dry.-H.	170	1.588	0.039	1.540	0.010	1.5	1.132	0.524
Myles	3	11	4.41	Dry.-H.	170	1.099	0.025	1.010	0.064	14.6	0.782	0.383
	4	12	4.64	Dry.-H.	170	1.099	0.027	0.936	0.136	29.3	0.782	0.386
	5	14	4.80	Dry.-CS.	170	1.099	0.026	0.950	0.123	25.6	0.782	0.315
	6	15	5.01	Dry.-CS.	170	1.222	0.030	1.005	0.187	37.2	0.870	0.315
	7	18	5.47	Dry.-CS.	170	1.222	0.029	1.048	0.144	26.3	0.870	0.358
	8	19	5.78	Dry.-CS.	170	1.344	0.050	1.199	0.095	16.4	0.958	0.399
	9	21	5.94	Dry.-H.	170	1.344	0.053	1.202	0.089	14.9	0.958	0.482
	10	22	6.19	Dry.-H.	170	1.466	0.045	1.093	0.328	52.9	1.044	0.327
	11	23	6.43	Dry.-H.	170	1.466	0.038	1.317	0.110	17.1	1.044	0.522
Jack	1	7	4.21	Dry.-H.	100	1.096	0.047	0.999	0.050	11.9	0.820	0.276
	2	8	4.52	Dry.-H.	100	1.096	0.041	0.719	0.336	74.3	0.820	0.217
	3	10	4.78	Dry.-H.	100	1.212	0.047	0.947	0.218	45.7	0.908	0.295
	4	11	5.03	Dry.-H.	100	1.327	0.054	1.021	0.252	50.1	0.994	0.337
	5	12	5.46	Dry.-H.	200	1.442	0.037	1.351	0.054	9.9	1.080	0.463
	6	14	5.64	Dry.-H.	200	1.442	0.040	1.164	0.238	42.1	1.080	0.348
	7	17	5.97	Pro.-H.	200	2.110	0.100	1.880	0.130	21.7	1.141	0.419
	8	18	6.36	Pro.-H.	200	2.110	0.121	1.626	0.363	57.1	1.141	0.413
Noel	1	15	6.30	Dry.-H.	0	1.500	0.039	1.474	−0.013	−2.0	1.124	0.509
	2	16	6.67	Dry.-H.	0	1.500	0.033	1.331	0.136	20.4	1.124	0.555
	3	18	7.10	Dry.-H.	0	1.615	0.031	1.402	0.182	25.7	1.210	0.600
	4	19	7.32	Dry.-H.	0	1.615	0.041	1.403	0.172	23.5	1.210	0.621
	5	20	7.63	Dry.-H.	200	1.584	0.026	1.484	0.074	9.7	1.188	0.649
	6	22	7.55	Dry.-H.	200	1.486	0.012	1.339	0.135	17.9	1.132	0.517
	7	25	7.63	Pro.-H.	200	2.110	0.106	1.780	0.224	29.3	1.141	0.515
	8	26	7.84	Pro.-H.	200	2.179	0.093	1.889	0.197	25.1	1.179	0.576

*E. LA., evaporated lactic acid milk; Evap., evaporated milk; Dry., dried half-skim milk; Pro., dried protein milk; Br., breast milk; H., honey; CS., corn syrup.

TABLE I—CONT'D

SUBJECT	PERIOD	AGE (WK.)	WT. (KG.)	FORMULA*	VITAMIN D (I.U.)	CALCIUM					PHOSPHORUS	
						INTAKE (GM./DAY)	URINE (GM./DAY)	FECES (GM./DAY)	RETENTION (GM./DAY)	RETENTION (MG./KG.)	INTAKE (GM./DAY)	FECES (GM./DAY)
Guy	1	7	3.83	Evap.-H.	170	0.540	0.022	0.401	0.117	30.5	0.365	
	2	9	4.10	Evap.-H.	170	0.540	0.012	0.361	0.167	40.7	0.365	0.088
	3	10	4.44	E. LA.-CS.	170	0.617	0.017	0.433	0.167	37.6	0.418	0.062
	4	12	4.76	E. LA.-H.	170	0.655	0.016	0.391	0.248	52.1	0.443	0.055
	5	14	5.08	E. LA.-H.	340	0.720	0.022	0.402	0.296	58.3	0.487	0.051
	6	15	5.32	E. LA.-CS.	340	0.745	0.024	0.449	0.272	51.1	0.504	0.071
	7	17	5.66	E. LA.-H.	500	0.771	0.033	0.427	0.314	55.5	0.521	0.047
	8	19	5.97	E. LA.-CS.	500	0.848	0.020	0.557	0.271	45.4	0.521	0.106
	9	20	6.33	E. LA.-CS.	500	0.874	0.029	0.570	0.275	43.4	0.590	0.167
	10	22	6.74	E. LA.-CS.	170	0.874	0.033	0.447	0.394	58.5	0.590	0.099
	11	24	6.99	E. LA.-CS.	170	0.874	0.037	0.461	0.376	53.8	0.590	0.107
Geoffery	1	8	4.22	Evap.-H.	170	0.617	0.042	0.386	0.188	44.6	0.418	0.101
	2	10	4.26	Evap.-H.	170	0.617	0.043	0.371	0.203	47.7	0.418	0.106
	3	11	4.54	E. LA.-CS.	170	0.694	0.042	0.442	0.210	46.3	0.470	0.064
	4	13	4.87	E LA.-H.	170	0.694	0.054	0.387	0.253	52.0	0.470	0.057
	5	15	5.15	E. LA.-H.	340	0.745	0.056	0.408	0.281	54.5	0.504	0.055
	6	16	5.36	E. LA.-CS.	340	0.745	0.064	0.406	0.276	51.4	0.504	0.056
	7	18	5.56	E. LA.-H	500	0.797	0.051	0.437	0.309	55.6	0.539	0.054
	8	20	5.83	E. LA.-CS.	500	0.900	0.056	0.621	0.223	38.2	0.609	0.132
	9	21	6.12	E. LA.-CS.	500	0.925	0.048	0.683	0.194	31.6	0.626	0.215
	10	23	6.44	E. LA.-CS.	170	0.951	0.060	0.662	0.229	35.6	0.644	0.121
	11	25	6.79	E. LA.-CS.	680	0.951	0.064	0.704	0.183	26.9	0.644	0.154
Nicky	1	12	3.74	E LA.-H.	0	0.542	0.035	0.406	0.102	27.2		
	2	13	3.92	E. LA.-CS.	0	0.567	0.029	0.520	0.016	4 2		
	3	15	4.13	E. LA.-H.	170	0.587	0.034	0.455	0.098	23.7		
	4	17	4.30	E. LA.-CS.	170	0.633	0.043	0.460	0.129	30.0		
	5	18	4.49	Evap.-CS.	170	0.633	0.030	0.520	0.082	18.4		
	6	20	4.69	Evap.-H.	170	0.716	0.029	0.446	0.242	51.5		
	7	23	5.34	Dryco and lactic acid.-H.	170	1.102	0.054	0.912	0.136	25.4		
	8	24	5.59	Dry.-CS.	170	1.259	0.059	1.047	0.153	27.4		
	9	28	6.17	Dry.-CS.	170	1.417	0.045	1.348	0.024	3.9		

Gus	1	9	4.00	E. LA.-H.	0	0.610	0.019	0.478	0.114	28.5		
	2	11	4.25	E. LA.-CS.	0	0.610	0.021	0.476	0.114	26.8		
	3	12	4.53	E. LA.-H.	170	0.633	0.038	0.372	0.223	49.3		
	4	14	4.74	E. LA.-CS.	170	0.678	0.039	0.431	0.208	43.8		
	6	17	5.21	Evap.-H.	170	0.788	0.023	0.537	0.227	43.6		
	7	20	5.58	Dryco and lactic acid.-H.	170	1.154	0.064	0.627	0.464	83.1		
	8	22	6.21	Dry.-CS.	170	1.312	0.074	1.022	0.217	34.9		
	9	25	6.55	Dry.-CS.	170	1.417	0.040	1.332	0.045	6.8		
Kenneth	1	8	4.15	Br.	170	0.174	0.010	0.145	0.018	4.4		
	2	9	4.37	Br.	170	0.173	0.012	0.114	0.048	10.9		
	4	13	5.26	Evap.-CS.	170	0.725	0.007	0.493	0.225	42.8		
	5	14	5.51	Evap.-H.	170	0.773	0.006	0.522	0.245	44.5		
	6	15	5.85	Evap.-H.	170	0.773	0.067	0.538	0.228	38.9		
	7	17	6.14	E. LA.-H.	170	0.797	0.019	0.494	0.285	46.3		
	8	19	6.43	E. LA.-CS.	170	0.797	0.025	0.487	0.286	44.4		
	9	20	6.81	Dry.-CS.	170	1.153	0.027	0.905	0.222	32.6		
Buddy	1	8	3.50	Br.	170	0.152	0.005	0.127	0.019	5.6		
	2	9	3.61	Br.	170	0.152	0.010	0.093	0.049	13.6		
	4	13	4.04	Evap.-CS.	170	0.580	0.006	0.510	0.064	15.7		
	5	14	4.30	Evap.-H.	170	0.677	0.006	0.551	0.119	17.7		
	8	19	4.95	E. LA.-CS.	170	0.761	0.010	0.513	0.238	48.0		
	9	20	5.01	Evap.-CS.	170	0.761	0.006	0.570	0.186	37.0		
	10	21	5.23	Evap.-H.	170	0.797	0.008	0.671	0.118	22.5		
Billy	1	8	4.73	Br.		0.207	0.006	0.141	0.060	12.7		
	2	10	5.15	Br.		0.207	0.009	0.100	0.098	19.1		
	3	11	5.43	Br.		0.207	0.008	0.106	0.093	17.1		

•E. LA., evaporated lactic acid milk; Evap., evaporated milk; Dry., dried half-skim milk; Pro., dried protein milk; Br., breast milk; H., honey; CS., corn syrup.

bath, and then in an electric oven maintained at 65° C. Aliquots of the urine for calcium analyses were evaporated and wet-ashed, while fecal aliquots were weighed on the analytical balance and ashed in a muffle furnace. Calcium determinations were done according to the method of Fiske and Logan.[1] Magnesium analyses for eighty-two periods were made on the filtrates from the calcium determinations and are reported elsewhere.[4] Phosphorus determinations were also done on some of the materials by the method of Fiske and Subbarrow.[2]

The detailed results for the 120 metabolism periods are reported in Table I. In addition to calcium intakes, excretion, and retention, the table includes data regarding the age, weight, and diet of the infant for each period. In order to evaluate the effect of honey, the data have been analyzed in various ways to facilitate our interpretation of results.

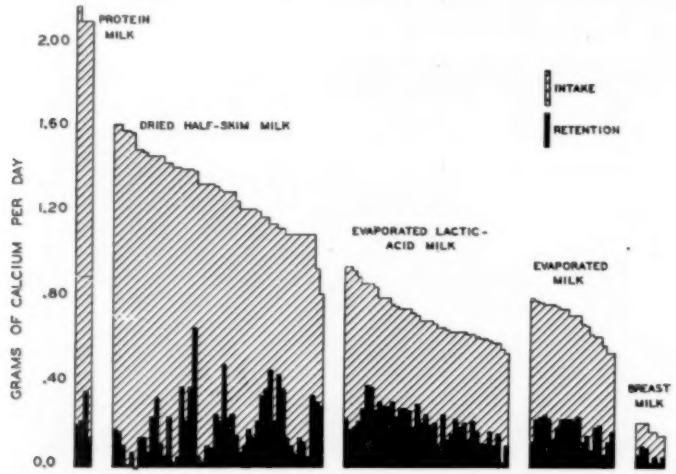

Chart 1.—Individual retentions of calcium in relation to calcium intakes. Each column represents results for one infant during one five-day metabolism period.

In Chart 1 the total daily retentions for the individual infants are arranged in relation to the calcium intakes for the different metabolic periods. The average milligrams of calcium retained per kilogram of body weight, for successively decreasing amounts of intake, were as follows: 24.6, 9.3, 35.0, 31.6, 28.9, 45.8, 40.6, 49.3, 43.4, 36.9, and 25.9. It is at once apparent that although there was a trend downward in retentions for lower levels of calcium intakes, higher levels of calcium gave unpredictable retentions which were not uniformly related in magnitude to the intakes. The greatest variability in results occurred when dried half-skim milk formulas were used and total retentions ranged from −0.013 to 0.659 Gm. per day. We can therefore conclude that low calcium intakes may limit calcium retentions, but high intakes do not insure high retentions.

In addition to the level of calcium intake, a second factor affecting calcium retentions was the amount and source of vitamin D. In Table II the average results have been calculated for each level of vitamin D

TABLE II

RETENTIONS OF CALCIUM IN RELATION TO VITAMIN D INTAKE

VITAMIN D (I. U.)	MILK	NO. OF PERIODS	CALCIUM RETENTIONS GM./DAY
1,000	Dried half-skim milk	2	0.298
1,000	Evaporated lactic acid milk	3	0.209
680	Dried half-skim milk	5	0.437
680	Evaporated milk	1	0.225
680	Evaporated lactic acid milk	1	0.183
500	Evaporated lactic acid milk	6	0.264
340	Evaporated lactic acid milk	4	0.281
200	Dried half-skim milk	4	0.125
170	Dried half-skim milk	31	0.169
170	Evaporated milk	19	0.178
170	Evaporated lactic acid milk	18	0.220
100	Dried half-skim milk	4	0.214
0	Dried half-skim milk	4	0.120
0	Evaporated lactic acid milk	7	0.120

administered with each type of milk. With some of the levels the number of cases is too small to permit valid conclusions, but certain trends in results have been observed. As was to be expected, the lowest retentions of calcium occurred when no supplementary vitamin D was given. The average low value of 0.120 Gm. of calcium per day was retained during eleven periods, when irradiated milk was the only source of vitamin D. This low average value of 0.120 Gm. was the same for both half-skim dried milk (four periods) and for evaporated milk (seven periods).

Cod-liver oil was the source of vitamin D for the three levels of 170, 340, and 680 units. When the vitamin D was increased from 170 to 680 units with the dried half-skim milk formulas, there was an increase in the average calcium retentions from 0.169 to 0.437 Gm. per day. An increase in vitamin D from 170 to 340 units with evaporated lactic acid milk formulas correlated with a smaller increase in retentions from 0.220 to 0.281 Gm. It will be noted that at 170 units, the 0.220 Gm. of calcium retained on evaporated lactic acid milk was considerably higher than the 0.169 Gm. figure obtained with dried half-skim milk. With plain evaporated milk plus 170 units of vitamin D, the retention average of 0.178 Gm. was between the results obtained with the other two types of milk on this amount of vitamin. With both plain evaporated milk and lactic acid evaporated milk, two cases at 680 units had relatively low retentions. These results are undoubtedly influenced by the level of calcium ingestion on these different types of milk, and by the inherent differences in individual infants. We can conclude that at low levels of vitamin D, higher retentions of calcium were observed with the

evaporated milks, especially evaporated lactic acid milk, than occurred with the dried half-skim milk; but at high levels of vitamin D intake, highest retentions were obtained with the dried milk.

A solution of a crystalline vitamin D preparation was used for the levels of 100, 200, and 1,000 units per day. Results here did not correlate with vitamin D intake as might have been anticipated, and the average retentions of calcium were lower than those for comparable levels of cod-liver oil. It may be that this preparation was not as potent in vitamin D content as would have been expected from its accompanying label, although discrepancies in results may partially have been due to inherent differences in individual infant types.

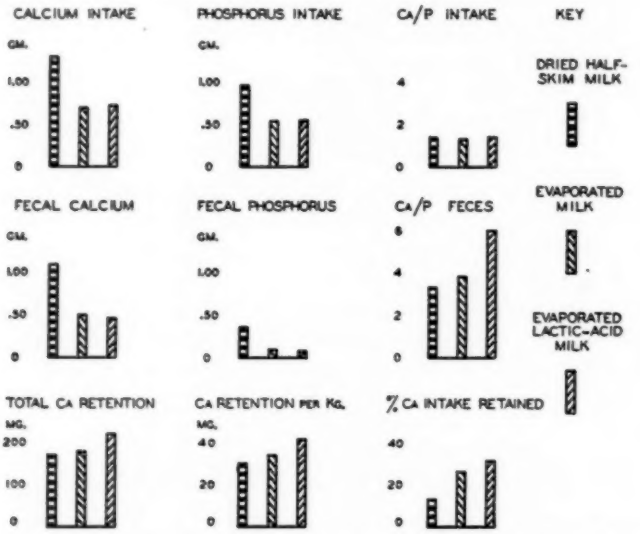

Chart 2.—Average results for all periods with 170 units of vitamin D.

To facilitate further evaluation of the data, Chart 2 has been prepared for the average results obtained with 170 units of vitamin D for each of the three types of milk studied. At this level of vitamin intake, significant numbers of cases were studied, and thirty-one metabolism periods were included in the averages for dried half-skim milk, while nineteen and eighteen periods, respectively, were studied for plain evaporated milk and evaporated milk plus lactic acid. The total calcium retentions for these milks were, as previously stated, 0.169, 0.178, and 0.220 Gm. per day. The retentions calculated per kilogram of body weight show the same trend, being 29.9 mg. for dried half-skim milk, 34.1 mg. for evaporated milk, and 41.2 mg. for the evaporated milk plus lactic acid. The lactic acid undoubtedly promoted favorable

conditions in the intestinal tract for calcium and phosphorus absorption. It is interesting to note how the processes of digestion and absorption have affected the Ca/P relationships. The ratios of the intakes of calcium and phosphorus average between 1.3 and 1.4 for all three milks. With dried half-skim milk periods, the Ca/P ratio in the feces has been moderately altered to 3.25. Plain evaporated milk periods give an average fecal Ca/P ratio of 3.85, indicating relatively greater absorption of phosphorus from the intestinal tract. With lactic acid evaporated milk periods, however, the ratio of Ca/P in the feces has shifted to 6.10, showing very efficient use of the ingested phosphorus. The increased efficiency in utilization of phosphorus correlates with the greater percentage of calcium intake which is retained during the lactic acid evaporated milk periods.

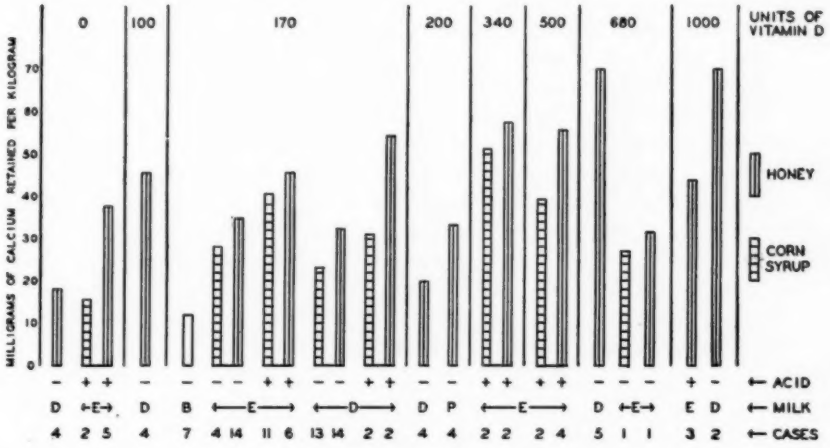

Chart 3.—Retention of calcium in relation to type of carbohydrate, amount of vitamin D, and use of lactic acid. *D*, dried half-skim milk; *E*, evaporated milk; *B*, breast milk; *P*, protein.

In the discussion thus far, we have commented upon how the level of calcium intake, the amount of vitamin D administered, the type of milk fed, and the use of lactic acid have affected the retentions of calcium. Although these factors are important, they are not the only ones which influenced the amount of calcium retained by the infants in this study. A significant factor was the type of carbohydrate used. In Chart 3 the data have been divided to show the effects of honey in contrast to results with corn syrup. Wherever bars join the honey and corn syrup columns, the same infants were fed under comparable conditions to make the comparison of these two types of carbohydrate completely valid. It will be noted that for all the paired periods studied, the average retention of calcium was always higher if honey had been included in the formula. These increased retentions when honey was

fed occurred both with low and with high intakes of vitamin D and occurred regardless of the type of milk fed or the use of lactic acid. Honey would seem, therefore, to have a definite beneficial influence upon the retention of calcium by young infants.

The uniform improved response with honey is of special interest in view of the variability in results observed for some of the other factors which affected calcium balances. Although a few individual infants had higher results on corn syrup when paired periods were compared, the majority of the infants had better results on honey, and the averages for all the paired periods were consistently in favor of honey.

In analyzing the data further, it is apparent that while the favorable influence of honey occurred regardless of what other factors were operating to affect the calcium retentions, the magnitude of improved response on honey tended to decrease as other beneficial factors were also employed. This is to be expected, since each infant has an upper level of response which is optimal for his storage of calcium. When a type of milk was fed which permitted adequate absorption of calcium and phosphorus, when higher levels of reliable vitamin D sources were given, or when lactic acid had been added to the milk, honey produced a lesser degree of response, but even with these factors operating to produce satisfactory retentions, the use of honey could still improve results.

In view of the results presented in this and previous papers, we conclude that honey is, indeed, a type of carbohydrate which is well suited to the infant's needs and therefore probably deserves a wider use in infant dietaries.

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THE INFLUENCE OF THE DIET OF THE NEWBORN INFANT ON THE PROTHROMBIN INDEX

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THE prothrombin index of the blood of newborn infants begins to fall shortly after birth and slowly returns to normal, although the statements concerning the degree and duration of the hypoprothrombinemia have varied greatly in several reports. Some observers have claimed that normal prothrombin indices were reached by the end of five days after birth and others, that normal values were not reached for ten days.

It occurred to us that the type of food might affect the prothrombin levels. Sanford, Morrison, and Wyatt in 1932[1] found that from the time they adopted the routine procedure of offering cow's milk formulas to infants, beginning four hours after birth, not a single instance of hemorrhagic disease had occurred throughout a two-year period of observation. They attributed the beneficial effects of this type of feeding to an increase of the fibrinogen levels of the blood. Since the time of their report, it has been determined that deficiencies in prothrombin are responsible for the majority of cases of so-called "hemorrhagic disease of newborn," and that vitamin K is the factor which stimulates the development of prothrombin. Quick and Grossman[2] have noted the inability of the newborn infant to maintain its stores of vitamin K after birth, and they thought that it was probable that the vitamin levels were restored later by synthetic action of bacteria which had invaded the intestinal tract. They surmised that early breast feeding of infants under less hygienic conditions than usually provided by hospitals, and therefore early development of the intestinal flora, might be conditions favoring a rapid development of the vitamin in the newborn infant.

The only experimental work in this field has been that of Salomonsen and Nygaard.[3] They compared the prothrombin levels of twelve infants who were placed at the breast twelve to twenty hours after birth, and of thirteen other infants who were breast fed on a similar schedule but received additional feedings of cow's milk mixtures beginning two hours after birth. The infants who received the early additional feedings did not develop the low prothrombin levels characteristic of the infants who received breast feedings only. We have extended the study of dietary influence by observing the prothrombin index in four groups of newborn infants, the groups differing in respect to the types of feeding and the times at which they were fed.

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METHODS

Determinations of the prothrombin clotting time were made by a microtechnique devised by Kato as a modification of the Quick method.[4] Rabbit brain was the source of thromboplastin.* The only change in the Kato procedure was the use of small test tubes 7 mm. in internal diameter and 15 mm. in length instead of hollow ground-glass slides. The prothrombin index was calculated as follows:

$$\frac{\text{Normal prothrombin time}}{\text{Infant's prothrombin time}} \times 100 = \text{Prothrombin index}$$

With the Kato method, the prothrombin time of the normal adult is 20 ± two seconds.

All of the infants studied were born in the obstetrical wards of the Cincinnati General Hospital during a period of five months from November, 1940, through March, 1941. Determinations of the prothrombin clotting time were made at birth or within an hour or two after birth and on each day thereafter for five days. None of the mothers or infants had received vitamin K.

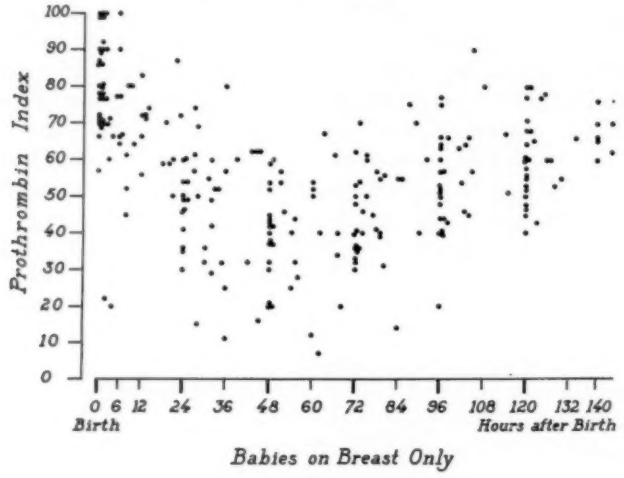

Fig. 1.

RESULTS

Group 1 included thirty-five infants who were put to the breast twelve hours after birth and at intervals of four hours thereafter. The prothrombin indices of each infant at birth and on the subsequent days of life have been plotted in Fig. 1. The average index at birth was 80.2, the lowest average was 37.2, and the average at the end of five days 61.2 (Table I). The individual determinations are plotted in Fig. 1.

*The thromboplastin was furnished by the Difco Co.

TABLE I

PROTHROMBIN INDICES IN FOUR GROUPS OF INFANTS

	AVERAGE PROTHROMBIN INDEX			AVERAGE HOUR AFTER BIRTH		
	FIRST VALUE	LOWEST VALUE	FINAL VALUE	FIRST VALUE	LOWEST VALUE	FINAL VALUE
Group 1 Breast fed only; thirty-five infants	80.2	37.2	61.2	-	57	121
Group 2 Breast fed plus additional breast milk; forty-six infants	78	56.1	74.5	-	48	115
Group 3 Breast fed with evaporated milk mixture added thirty-six hours after birth; thirty-seven infants	82.1	54.8	95.4	-	39	110
Group 4 Breast fed with evaporated milk mixture added twelve hours after birth; eighty-one infants	78	65.1	93.1	-	24	92

Group 2 included forty-six infants who followed the same schedule of breast feeding but received additional feedings of breast milk after each regular nursing. The additional breast milk was obtained by pumping the fully functioning breasts of other mothers who had been nursing

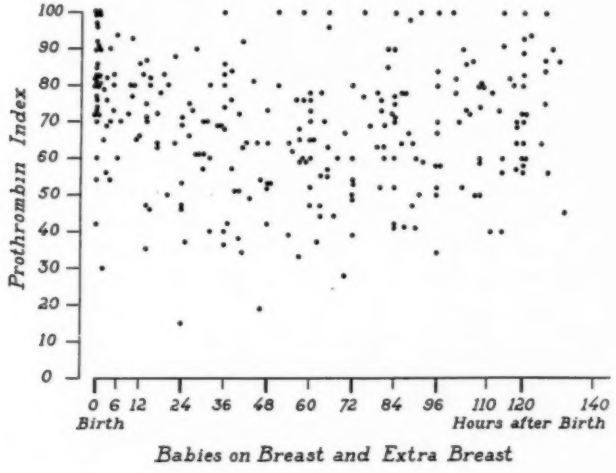

FIG. 2.

their infants for a week or more. This milk was pooled and boiled before offering it to the infants of the experimental group. The average prothrombin index at birth was 78 in this group, the lowest average was 56.1, and the average at the end of five days was 74.5 (Table I). Individual determinations appear in Fig. 2.

Group 3 included thirty-seven infants who followed the same schedule of breast feeding as the first two groups but at the thirty-sixth hour of life received additional feeding of a mixture containing 6 oz. of evaporated milk, 12 oz. of water, and 1 oz. of karo syrup. Approximately two ounces of this mixtures were offered after each breast feeding for a period of two days. The average prothrombin index at birth was 82.1, the lowest average was 54.8, and the average value at the end of five days was 95.4 (Table I). The individual indices are plotted in Fig. 3.

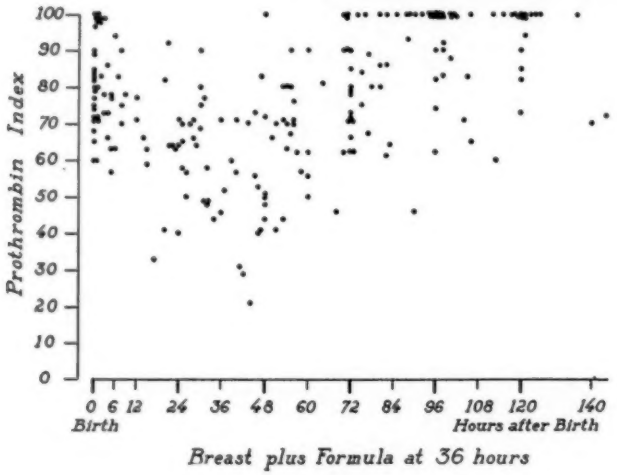

Fig. 3.

Group 4 included eighty-one infants who followed the same schedule of breast feeding as the previous groups but were given two ounces of the evaporated milk mixture already mentioned, after each breast feeding, beginning twelve hours after birth and continued for the next two days of life. These infants had an average prothrombin index of 78 at birth, a lowest average of 65.1, and a final average of 93.1 at the end of five days (Table I). Fig. 4 represents the separate determinations.

The data from all four groups have been compared in Table I, together with the time at which the average low values and average final values were reached. This information has been represented graphically in Fig. 5.

The average initial determinations were approximately the same in all four groups. The infants in Group 1 who received no food other than breast milk developed the lowest average prothrombin index, 37.2, and this level was reached at about fifty-seven hours. Additional food, consisting of breast milk and started twelve hours after birth, seemed to halt the decline of the prothrombin index, and recovery began sooner.

The evaporated milk mixture, started thirty-six hours after birth, was no more effective than early additional breast milk feedings in preventing the low prothrombin levels (average, 54.8) but hastened recovery. The best results, however, were obtained when an evaporated milk mixture was offered after each nursing, beginning twelve hours after birth and continued for two days, as illustrated by the fourth group of infants, whose average prothrombin index dropped to only 65.1 and after twenty-four hours had started upward again.

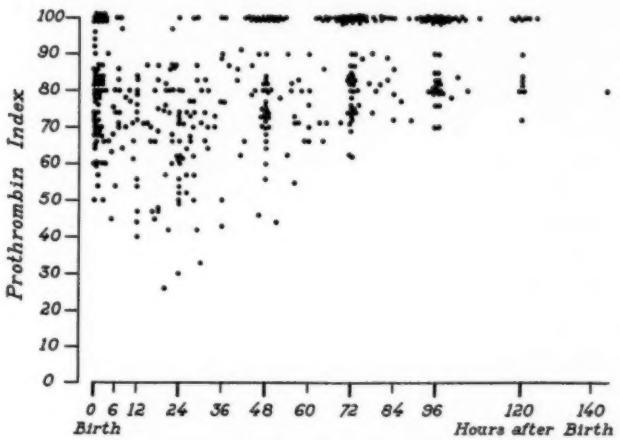

Fig. 4.

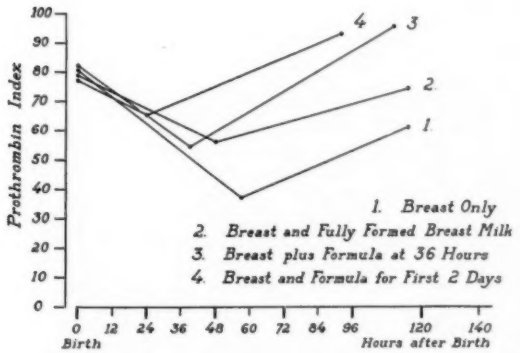

Fig. 5.

Nine of the group of thirty-five who nursed at the breast alone regained their initial prothrombin indices during the period of observation and none of this group reached 100 (Table II). Of the forty-six infants who received additional breast milk, twenty regained their initial levels,

and seven reached values of 100. Of the thirty-seven who received evaporated milk mixtures beginning thirty-six hours after birth, thirty-five regained their initial values and twenty-nine of these reached 100. Of the eighty-one infants who received the additional feedings of an evaporated milk mixture twelve hours after birth and continuing for two days, seventy-four regained their initial levels during the five-day period of observation, and fifty-two of these reached indices of 100.

TABLE II

PATIENTS REGAINING INITIAL VALUES AND REACHING 100 PER CENT OF NORMAL WITHIN FIVE DAYS

	NUMBER OF INFANTS	
	REGAINED INITIAL VALUE	REACHED 100%
Group 1 Breast fed only; thirty-five infants	9	0
Group 2 Breast fed plus additional breast milk; forty-six infants	20	7
Group 3 Breast fed with evaporated milk mixture added thirty-six hours after birth; thirty-seven infants	35	29
Group 4 Breast fed with evaporated milk mixture added twelve hours after birth; eighty-one infants	74	52

TABLE III

CHANGE IN PROTHROMBIN INDEX CALCULATED AS PERCENTAGE OF INITIAL VALUE

	MAXIMUM LOSS AS % OF FIRST VALUE	FINAL VALUE AS % OF FIRST VALUE
Group 1 Breast fed only; thirty-five infants	52.3	78.3
Group 2 Breast fed plus additional breast milk; forty-six infants	28.4	97.1
Group 3 Breast fed with evaporated milk mixture added thirty-six hours after birth; thirty-seven infants	33.6	118.1
Group 4 Breast fed with evaporated milk mixture added twelve hours after birth; eighty-one infants	19.9	123.2

Another method of evaluating the response of the four groups of infants to the different types of feeding was the determination of the loss and gain of prothrombin in terms of the prothrombin levels at birth. As shown in Table III, the infants who received only breast milk lost an average of 52.3 per cent of their initial levels, and by the fifth day their indices had reached 78.3 per cent of their initial levels. More favorable indices were maintained by the infants in Groups 2 and 3,

but again the best response was made by the group of infants who received early additional feedings of the evaporated milk mixture. The average prothrombin index in this group of infants declined only 19.9 per cent and rose subsequently to higher levels than were present at birth (123.2 per cent).

DISCUSSION

The results of this study indicate that the type of feeding and the time of initiating additional feeding during the first few days of an infant's life influence the trend of the prothrombin index. Additional feedings of breast milk prevented the marked degrees of hypoprothrombinemia which were observed in infants who were breast fed by their mothers only. Early additional feeding of an evaporated milk mixture resulted in the smallest decline of the prothrombin index and the quickest recovery to normal values, whereas early feedings of breast milk and later feedings of evaporated milk were not so effective.

We shall not attempt to explain the mechanism by which early additional feedings affect the prothrombin levels until further study of the possible factors involved. It is obvious that such additional feeding does not equal the effect of vitamin K therapy in producing a rapid rise in prothrombin levels.

This study may offer an explanation for the variations of the course of prothrombin indices of the newborn infant noted by other observers. Unless the nature of the neonatal feeding regimen is stated, it is difficult to compare the reports of one author with those of another. Possibly other environmental factors besides feeding influence the natural trend of prothrombin, and therefore the conditions under which each experiment is carried out should be fully stated.

SUMMARY

The course of the prothrombin index of four groups of newborn infants was influenced by the type of feeding offered during the first few days of life.

The group of infants fed at the breast every four hours, beginning twelve hours after birth, showed the greatest decline in their prothrombin indices and the most prolonged recovery to initial levels.

The group of infants who received bottle feedings of fully formed breast milk after each breast feeding, on the same time schedule, showed a less marked drop in their prothrombin indices and a more rapid recovery than the first group.

Better results were obtained in a third group of infants who received additional feedings of evaporated milk started thirty-six hours after birth.

The fourth group of infants who received additional feedings after each nursing, beginning twelve hours after birth, showed the least decline in prothrombin indices and the most rapid recovery to normal values.

In studies of the behavior of the prothrombin index of newborn infants, it is important to record the type and schedule of feeding so that the results of one observer may be compared accurately with those of another.

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PROTHROMBIN IN THE NEWBORN INFANT

IV. Further Observations on the Prothrombin Response to Intravenous Administration of Water-Soluble Naphthoquinone

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INTRODUCTION

IT IS now definitely established that a hypoprothrombinemia exists in the neonatal period.[1-7] In addition to vitamin K from natural sources, certain naphthoquinone derivatives have been found effective in initiating an elevation of prothrombin concentration in hypoprothrombinemic infants.[8-11] Detailed knowledge of the nature of the prothrombin response to the administration of naphthoquinone is of utmost importance in view of the relationship of hemorrhagic disease of the newborn to this hypoprothrombinemic state.

The antihemorrhagic quinone derivatives may be administered by three routes: oral, subcutaneous, and intravenous. The response to the oral and subcutaneous routes in hypoprothrombinemic infants was studied by Poncher and Kato, employing their microprothrombin method.[8] Determinations were performed by them after two hours, six hours, and twenty-four hours, and daily thereafter for several days. The results indicated a definite prothrombin elevation in a few cases within two hours and in the majority of cases within six hours. Normal values were reached within twenty-four hours and were maintained thereafter for several days.

Observations upon the character of prothrombin response in hypoprothrombinemic infants to the intravenous administration of naphthoquinone were reported by us in a previous article.[11] The superiority of this route of therapy was demonstrated by the rapid initial prothrombin response. One milligram of 2-methyl-1, 4-naphthoquinone in soluble form was administered intravenously to several infants who exhibited various grades of severity of prothrombin deficiency. Prothrombin determinations were performed thereafter at frequent short intervals for several hours. In every case a definite elevation in prothrombin concentration was demonstrable within two hours. However, in the individual cases the interval varied from within one-half hour in one case, within one hour in two cases, and within two hours in one case from the administration of the quinone until the prothrombin response became manifest.

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PURPOSE OF STUDY

This investigation was undertaken, first, to determine whether the intravenous administration of a larger dosage of a soluble form of 2-methyl-1, 4-naphthoquinone than had been used in the previous study would result in further hastening the initial prothrombin elevation; and second, because it was felt that a study upon a larger group of infants would be of value in determining whether the rapid response to intravenous naphthoquinone therapy is a constant phenomenon in hypoprothrombinemia of newborn infants.

This information is definitely necessary in establishing the preferable therapeutic route of naphthoquinone administration for the treatment of hemorrhagic disease of the newborn. Obviously the method which produces a prothrombin elevation within the shortest period of time is to be preferred over others.

METHOD OF STUDY

Prothrombin determinations were performed on fifty-four normal newborn infants chosen at random. The results are recorded in Table I. Of these, ten who represented the various degrees of hypoprothrombinemia from moderate to severe were chosen for the study. Two milligrams of 2-methyl-1, 4-naphthoquinone in soluble form* were administered intravenously into a scalp vein of each of these ten infants. Prothrombin determinations were then performed after one-half, one, one and one-half, two, and three hours. In addition, a determination was done after twenty-four hours or at a varying interval thereafter in each case.

As in the previous investigations, the prothrombin clotting time was determined by the method of Quick[12] because of its greater accuracy over that of the various microprothrombin methods which have been proposed. The disadvantage of having to secure blood from the external and internal jugular veins of newborn infants may be overcome easily with a little training.

Two and one-quarter cubic centimeters of blood were added to ¼ c.c. of 0.1 sodium oxalate, and the plasma was removed after centrifuging. To 0.1 c.c., of the plasma was added 0.1 c.c. of thromboplastin (prepared as suggested by Quick). By blow pipette, 0.1 c.c. of 0.025 M calcium chloride was added, and the time required for the formation of a clot was recorded by stop watch. The temperature of the solutions was maintained at 37.5° C. by the use of a water bath.

The results were expressed in terms of prothrombin clotting time and prothrombin concentration. The latter value was estimated from the curves constructed of the prothrombin clotting times of serial dilutions of the normal adult plasma for each of the thromboplastin preparations employed. The term prothrombin concentration is

*The preparation employed was 2-methyl-1, 4-naphthohydroquinone-3-sodium sulfonate and was supplied by Abbott Laboratories. An ampule of 1 c.c. containing 3.2 mg. of the naphthohydroquinone and corresponding to 2 mg. of 2-methyl-1, 4-naphthoquinone was used in each case.

TABLE I

PROTHROMBIN DETERMINATIONS ON FIFTY-FOUR NORMAL NEWBORN INFANTS

CASE	AGE (HR.)	PROTHROMBIN CLOTTING TIME OF UNDILUTED PLASMA (SEC.)	PROTHROMBIN CONCENTRATION (% OF NORMAL)
	Normal adults	11½	100
1	18	15	44
2	15	15	44
3	10	13	70
4	29	15	44
5	74	40	9
6	80	300+	< 3
7	106	28	14
8	36	19	25
9	103	13	70
10	108	16½	35
11	60	17½	30
12	78	16½	35
13	27	15½	40
14	58	12	90
15	51	17½	30
16	23	42	9
17	82	24	17
18	63	20	23
19	83	20	23
20	75	15	44
21	60	11½	100
22	11	22	19
23	58	14½	47
24	36	44	8
25	108	19½	23
26	14	15½	40
27	38	20½	21
28	58	15½	40
29	27	31	33
30	34	62	6
31	47	14	50
	Normal adults	12½	100
32	106	15	50
33	59	14	66
34	104	14	66
35	47	25	23
36	107	17	42
37	59	13	90
38	44	17	42
39	55	23	27
40	31	19	35
41	25	15	50
42	26	25	23
43	26	17	42
44	58	14	66
45	31	18	38
46	52	17	42
47	59	21	30
48	108	17	42
49	21	17	42
50	52	15	50
51	132	14	66
52	110	15	50
53	32	22	18
54	25	20	33

TABLE II

RESPONSE OF TEN NORMAL NEWBORN INFANTS WITH VARIOUS DEGREES OF HYPOPROTHROMBINEMIA TO INTRAVENOUS ADMINISTRATION OF 2 MG. OF 2-METHYL-1, 4-NAPHTHOQUINONE IN SOLUBLE FORM

INFANT (CASE NO.)	AGE (HR.)	2-METHYL-1, 4-NAPHTHOQUINONE INTRAVENOUSLY	TIME AFTER THERAPY (HR.)	PROTHROMBIN CLOTTING TIME (SEC.)		PROTHROMBIN CONCENTRATION (% OF NORMAL)	
				UNDILUTED PLASMA	PLASMA DILUTED 50%	ESTIMATED FROM UNDILUTED PLASMA	ESTIMATED FROM PLASMA DILUTED 50%
5	74	2 mg.	½	40	59	9	10
			1	24	40	17	18
			1½	20	30	23	26
			2	17	25	32	32
			3	15	20	44	46
				14	19	50	50
Normal adults				11½	14	100	100
6	80	2 mg.	½	300+	No Clot	< 3	< 3
			1	300+	No Clot	< 3	< 3
			1½	44	92	8	7
			2	25	47	16	16
			3	21	34	21	22
				20	31	23	24
Normal adults				11½	14	100	100
7	106	2 mg.	½	28	46	14	16
			1	22	35	19	22
			1½	21	33	21	24
			2	21	34	21	22
			3	21	34	21	22
				20	32	23	24
Normal adults				11½	14	100	100
16	23	2 mg.	½	42	70	9	10
			1	42	74	9	10
			1½	41	68	9	10
			2	26	43	15	17
			3	22	36	19	20
				21	34	21	22
Normal adults				11½	14	100	100
17	82	2 mg.	½	24	43	17	16
			1	19	31	25	26
			1½	19	32	25	24
			2	19	31	25	26
			3	19	31	25	26
				19	33	25	24
Normal adults				11½	14	100	100
24	36	2 mg.	½	44	83	8	8
			1	43	86	8	8
			1½	23	38	18	20
			2	23	39	18	20
			3	23	41	18	18
				22	37	19	20
Normal adults				11½	14	100	100

TABLE II—CONT'D

INFANT (CASE NO.)	AGE (HR.)	2-METHYL-1, 4-NAPHTHOQUINONE INTRAVENOUSLY	TIME AFTER THERAPY (HR.)	PROTHROMBIN CLOTTING TIME (SEC.)		PROTHROMBIN CONCENTRATION (% OF NORMAL)	
				UNDILUTED PLASMA	PLASMA DILUTED 50%	ESTIMATED FROM UNDILUTED PLASMA	ESTIMATED FROM PLASMA DILUTED 50%
30	34			62	155	6	6
		2 mg.	½	64	165	6	6
			1	30	54	13	14
			1½	27	49	14	16
			2	25	46	16	16
			3	22	36	19	20
Normal adults				11½	14	100	100
35	47			25	42	23	22
		2 mg.	½	25	41	23	22
			1	25	43	23	22
			1½	21	35	30	28
			2	21	35	30	28
			3	19	29	36	38
Normal adults				12½	15	100	100
39	55			23	37	27	26
		2 mg.	½	23	36	27	28
			1	23	37	27	26
			1½	19	28	36	40
			2	19	30	36	36
			3	19	29	36	38
Normal adults				12½	15	100	100
42	26			25	43	23	22
		2 mg.	½	25	41	23	24
			1	21	35	30	28
			1½	19	29	36	38
			2	19	28	36	40
			3	18	28	38	40
Normal adults				12½	15	100	100

really a summation of its concentration and its convertibility to thrombin in the clotting mechanism rather than a true quantitative estimation of prothrombin. With each group of determinations normal adult controls were used. In this study two thromboplastin preparations were employed; one producing clotting in eleven and one-half seconds, and the other in twelve and one-half seconds for the undiluted plasma of normal adults. With each specimen of blood drawn from the ten infants, prothrombin clotting times were determined for both undiluted plasma and plasma diluted with an equal quantity of physiologic saline. This was done to insure increased accuracy.

The infants chosen for the study possessed initial prothrombin clotting times varying from twenty-three seconds to well beyond 300 seconds. Expressed in terms of prothrombin concentration, the values ranged from 27 per cent to less than 3 per cent.

RESULTS

In Tables II and III, and Figs. 1 and 2 are presented the results of the study. Within one and one-half hours after the intravenous administration of the naphthoquinone all ten infants manifested a definite

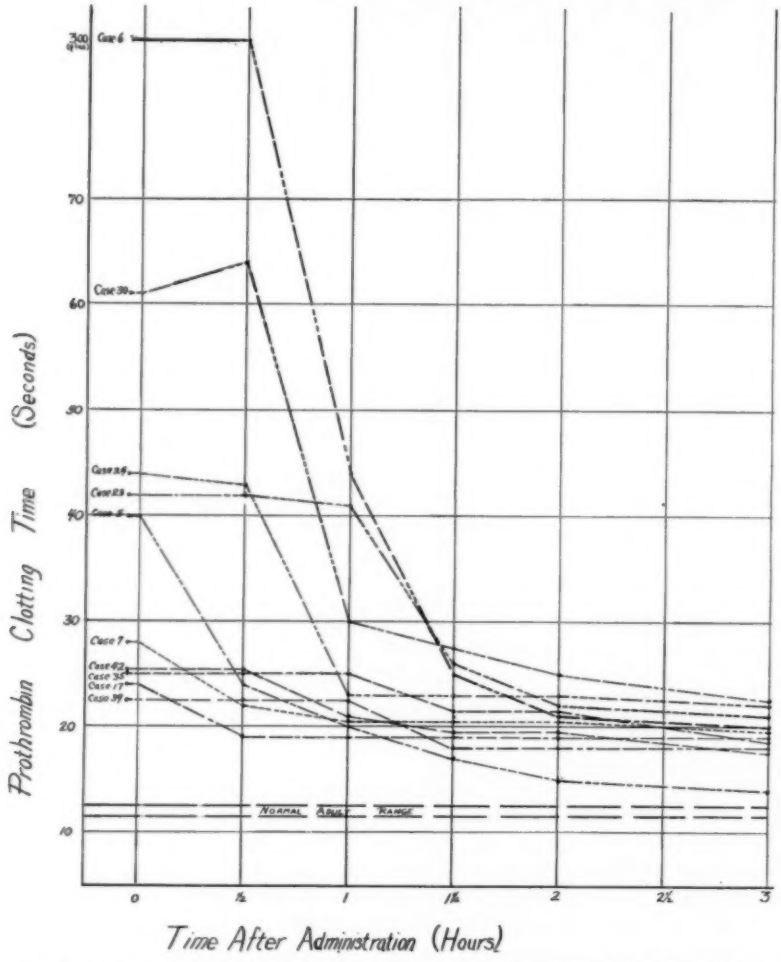

Fig. 1.—Effect upon the prothrombin clotting time of intravenous administration of 2 mg. of 2-methyl-1, 4-naphthoquinone in soluble form in ten newborn infants with hypoprothrombinemia of various degrees of severity.

decrease in prothrombin clotting time (elevation in prothrombin concentration). Of these, three responded within one-half hour, four within one hour, and the remaining three within one and one-half hours.

As in the previous study,[11] there was no relationship between the severity of the hypoprothrombinemia and the rapidity of the initial prothrombin response.

In addition, as was found in the previous investigation, the infants' prothrombin clotting times which had been markedly prolonged prior to therapy decreased precipitously with the first response.

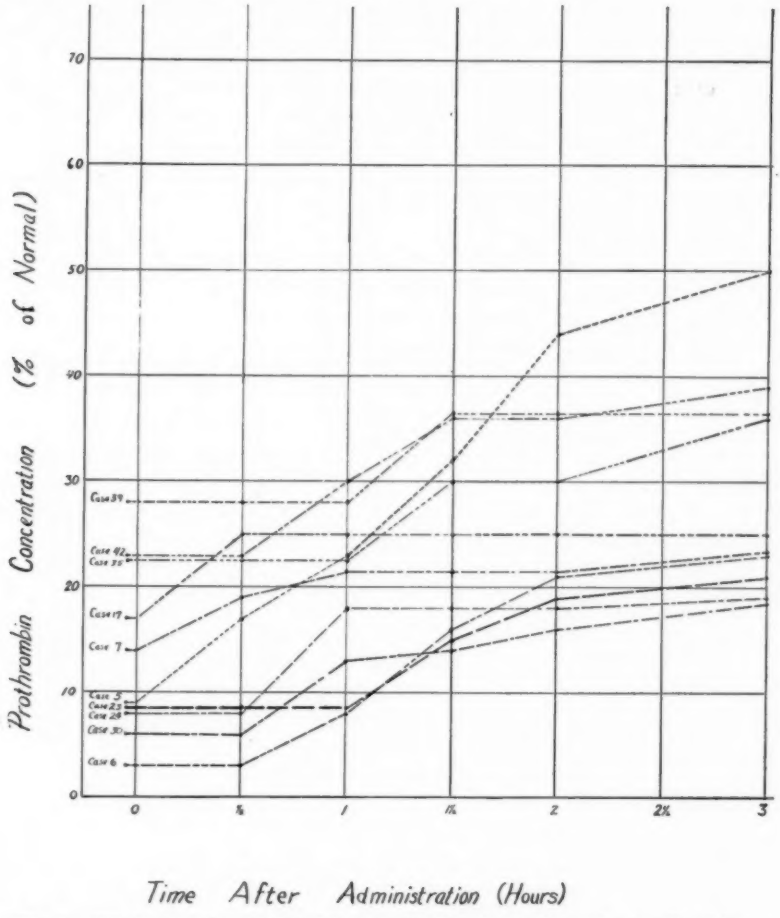

Fig. 2.—Effect upon the prothrombin concentration (percentage of normal) of intravenous administration of 2 mg. of 2-methyl-1, 4-naphthoquinone in soluble form in ten newborn infants with hypoprothrombinemia of various degrees of severity.

Within twenty-four hours and for the several days thereafter, the prothrombin concentration was maintained within the normal range of 70 per cent to 100 per cent, as shown in Table III.

In those infants with original moderate hypoprothrombinemia, the prothrombin concentration was higher after several hours than in those infants who originally had a severe hypoprothrombinemia as shown in Fig. 2. This was our experience in the previous study as well. Of the seven infants with a prothrombin concentration of 17 per cent

TABLE III

FOLLOW-UP PROTHROMBIN DETERMINATIONS UPON THE TEN HYPOPROTHROMBINEMIC NEWBORN INFANTS WHO HAD RECEIVED INTRAVENOUSLY ONE DOSAGE OF 2 MG. 2-METHYL-1, 4-NAPHTHOQUINONE IN SOLUBLE FORM

CASE	TIME AFTER THERAPY (DAYS)	PROTHROMBIN CLOTTING TIME (SEC.)		PROTHROMBIN CONCENTRATION (% OF NORMAL)	
		UNDILUTED PLASMA	PLASMA DILUTED 50%	ESTIMATED FROM UNDILUTED PLASMA	ESTIMATED FROM PLASMA DILUTED 50%
5	2	12½	15	100	100
6	2	14	18½	70	74
7	2	14	18½	70	74
16	1	14	18	70	78
17	1	13½	17	80	84
24	5	13½	16½	80	88
30	5	13	17	90	84
35	8	13	15	90	100
39	3	13½	17	80	84
42	3	13	16½	90	96
Normal adults		12½	15	100	100

or less, it was found that after three hours only one had reached a value above 25 per cent. The remaining three patients with initial values ranging between 23 per cent and 27 per cent attained levels above 35 per cent during the same period.

No untoward effects were observed from the use of this large dosage of the naphthoquinone.

In none of these infants was there any clinical evidence of hemorrhagic disease, regardless of the severity of prothrombin deficiency. This appears to bear out the evidence which has been accumulating to the effect that prothrombin deficiency in itself is not sufficient to produce hemorrhagic disease of the newborn.

CONCLUSIONS

From this study it appears that in hypoprothrombinemic newborn infants a prothrombin elevation may be expected constantly within one and one-half hours following the intravenous administration of 2 mg. of 2-methyl-1, 4-naphthoquinone in soluble form. In the previous investigation,[11] the intravenous administration of 1 mg. of the naphthoquinone produced a response within one hour in three of the four infants studied. The remaining infant responded within two hours. However, in view of the fact that no determination was performed at the one and one-half hour interval, the probability arises that this infant, as well, may have shown a prothrombin response at the one and one-half hour interval.

It appears, therefore, that a dosage of 1 mg. is adequate and that a dosage of 2 mg. in all likelihood is more than is necessary. This con-

clusion is not surprising considering the fact that 2 mg. for a newborn infant of 7 pounds corresponds, in terms of body weight, to about 40 mg. for an adult of 150 pounds. Two milligrams is the effective intravenous dosage of 2-methyl-1, 4-naphthoquinone in adults.[13]

Following the initial prothrombin response, progressive elevation of the prothrombin concentration may be expected to continue. Normal values are reached within twenty-four hours and are maintained at this level for several days thereafter.

There is no relationship between the severity of hypoprothrombinemia and the rapidity of the initial prothrombin response within the one and one-half hour period during which an effect will be manifest, following naphthoquinone therapy.

Three hours following the intravenous use of the 2 mg. dosage of the naphthoquinone, the prothrombin concentrations reached by newborn infants are no higher than those reached by the use of the 1 mg. dosage, which was employed in the previous investigation.

COMMENT

The data presented in this investigation indicate that a procedure is available to us which most probably is the one of choice in the treatment of hemorrhagic disease of the newborn. The intravenous administration of from 1 to 2 mg. of 2-methyl-1, 4-naphthoquinone in soluble form in hypoprothrombinemic newborn infants will result in prothrombin elevation at some time within one and one-half hours. It would follow, therefore, that the intravenous route of naphthoquinone administration is the preferable procedure in the treatment of hemorrhagic disease of the newborn. Certainly, the intravenous route is preferable to the oral or subcutaneous routes which, in most cases, have been shown to produce a prothrombin elevation only within six hours. A delay of several hours in the prothrombin response exposes an infant with hemorrhagic disease to the ever-present danger of a sudden massive hemorrhage which may involve a vital organ. The intravenous route of administration hastens the response and diminishes the possibility of this undesirable occurrence.

It may be well to reiterate the importance of making arrangements for transfusion in addition to administering the naphthoquinone. This precaution may prevent a fatality if a sudden hemorrhage should precede the prothrombin response. If the bleeding ceases or if the blood loss is of no significance, transfusion need not be given.

SUMMARY

The effect in hypoprothrombinemic newborn infants of intravenous administration of a large dosage of 2-methyl-1, 4-naphthoquinone in soluble form was studied.

Of fifty-four normal newborn infants, ten who exhibited the various degrees of prothrombin deficiency, from moderate to severe, were chosen as subjects.

Two milligrams of 2-methyl-1, 4-naphthoquinone in soluble form were administered intravenously to each of these ten infants. Prothrombin determinations, using Quick's method, were performed after one-half, one, one and one-half, two, and three hours. An additional determination was done after twenty-four hours or at a varying interval thereafter.

Within one and one-half hours all ten infants showed a definite prothrombin elevation.

However, in the individual cases, variations, in the rapidity of response occurred. Three infants responded within one-half hour, four more within one-hour, and the remaining three within one and one-half hours.

Within twenty-four hours the prothrombin concentration was within the normal range of 70 per cent to 100 per cent and was maintained thereafter for the several days studied.

There appeared to be no relationship between the rapidity of the initial prothrombin response and the degree of severity of hypoprothrombinemia.

Three hours after therapy the prothrombin concentration of those infants with an original moderate hypoprothrombinemia was at a higher level than in those who originally had a severe hypoprothrombinemia.

A dosage of 2 mg. of 2-methyl-1, 4-naphthoquinone in soluble form administered intravenously produces a prothrombin response in hypoprothrombinemic infants no more rapidly than a dosage of 1 mg.

The intravenous administration of from 1 to 2 mg. of 2-methyl-1, 4-naphthoquinone in soluble form produces a prothrombin elevation within one and one-half hours in hypoprothrombinemic newborn infants. It would follow, therefore, that the intravenous route of naphthoquinone administration is the preferable procedure in the treatment of hemorrhagic disease of the newborn. Preparations for transfusion should be made at the same time so that blood may be given without delay if the necessity should arise.

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MISCELLANEOUS NOTES ON RATBITE FEVER

Report of Two Cases; Review of American Reports From 1931 to 1940; Observations on the Isolation of Spirillum Minus; and Results of Standard Serologic Tests During Ratbite Fever

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THIS communication is prepared to present several specific aspects of ratbite fever, and the reader is referred to the contributions of Bayne-Jones,[2] McDermott,[26] and Solomon[31] for more detailed surveys of the clinical and epidemiologic features.

Wilcox,[35] in 1840, recorded a group of symptoms that followed the bite of a rat, but it was not until 1917 that Futaki and his co-workers[13] described *Spirillum minus (Spirochaeta morsus muris)* as the organism responsible for a disease entity, ratbite fever.* Although of minimal epidemiologic importance in this country, it is of frequent enough occurrence to warrant more attention than it has received. The salient clinical data are:

1. The bite of a rat or other infested animal.
2. An incubation period of one to five weeks.
3. Then a chancroid exacerbation at the site of insult with lymphadenitis dependent to that area.
4. This is accompanied by systemic manifestations: recurrent bouts of fever, often a macular rash, and varying degree of prostration and debility.
5. A polymorphonuclear leucocytosis and secondary anemia are frequently present. The Kahn and similar reactions tend to become positive during the course of the disease, while the Wassermann reaction is rarely affected, a point discussed in detail later.
6. Treatment with arsenicals commonly employed against syphilis is highly successful, and the prognosis for complete recovery is excellent with adequate therapy. A mortality of 10 per cent, commonly quoted for untreated cases, appears justified by the severity of symptoms noted in certain instances.
7. Septicemia due to the Haverhill group, tularemia, brucellosis, and infection with pyogenic organisms enter the differential diagnosis.

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*Our attention has been called to a statement by Dawson and Hobby,[8] that there is room for doubt as to the etiologic significance of *S. minus*. This is based primarily upon the fact that streptobacilli and similar organisms have been recovered from the blood stream in patients sick following the bite of a rat. We are inclined to interpret this as meaning (1) that two relatively similar syndromes exist, one due to *S. minus*, and the other to the streptobacillus, as has been adequately discussed by Allbritten and his collaborators, or (2) that infection with the two organisms may be received concomitantly. That the spirillum is not the cause of ratbite fever seems fantastic to us for a number of reasons, including the fact that the disease has been reproduced in human beings by inoculation with the spirillum and that a disease can be produced in guinea pigs which simulates that in man on most details.

CASE REPORTS

CASE 1.—(I. H., No. 22279.) This case is of interest because of the age of the patient and the ease with which the diagnosis was confirmed.

At 6 weeks of age this baby sustained a wound to the bridge of the nose, attributed to the bite of a rat. Two weeks later, swelling of the face, a red macular eruption, a fever, cough, and pallor were noted. The swelling soon subsided, but fever, accompanied by a diffuse rash, recurred intermittently. When the patient was hospitalized two months after the beginning of symptoms, the liver and spleen were easily palpated, and while her nutrition appeared unaffected, she was quite pale. No local lesion was evident, and there was no eruption. Laboratory data included: (1) white blood cells, 21,000 per cubic millimeter with 64 per cent polymorphonuclear forms; (2) red blood cells, 2,000,000 per cubic millimeter with hemoglobin 55 per cent of normal; (3) Hinton test positive, Wassermann negative, and serology of both parents negative.

The temperature was 102° F. on admission and continued to be elevated during the next two weeks but without the rhythmic periodicity usually associated with the disease, a finding probably attributable to her age and the development of bronchitis. Blood was taken on three occasions for animal inoculation and treatment started with neoarsphenamine. She received nine injections at four-day intervals, beginning with 5 mg. per kilogram of body weight and gradually increasing to 20 mg. The temperature remained normal after the second injection, and a transfusion was given to correct the anemia. Hinton tests were positive persistently until one month after the last injection of neoarsphenamine, and negative reactions were recorded for one year.

Absence of enlarged superficial nodes in this patient necessitated the use of blood to isolate *S. minus*. Five cubic centimeters, withdrawn while her temperature was 102° F., were injected subcutaneously into each of three guinea pigs. The organisms were found in their typical form by the seventeenth day in each instance.

CASE 2.—(University of Oregon, No. 108828.) This case is of interest primarily as the first instance of infection from the Pacific Northwest.

A 6-year-old boy, who was bitten on the right index finger by a rat in March, 1940, developed swelling at the site of injury and dependent adenopathy two weeks later. Daily episodes of rigor and fever, accompanied on one occasion by a macular eruption, appeared and persisted intermittently until the time of hospitalization four weeks later. Local swelling and enlarged axillary nodes were still present, but there was no eruption, and the spleen could not be felt. Laboratory data included: (1) white cell count, 6,700 per cubic millimeter with 73 per cent polymorphonuclear forms; (2) red blood cells, 4,500,000 per cubic millimeter with 71 per cent of normal hemoglobin; (3) Kahn and Kline tests strongly positive, and maternal serology negative.

The temperature was 103.2° F. on admission and reached 104° F. the following day. A lymph node was removed for animal inoculation, and the child was discharged because of exposure to measles. Treatment with neoarsphenamine was instituted at home, and there were no further bouts of fever. The Kahn reaction was negative six weeks after the first injection of neoarsphenamine. Diagnosis was confirmed in this instance by emulsifying a piece of lymph node in saline and injecting 5 c.c. lots subcutaneously into guinea pigs. The animals showed enlarged inguinal glands on the fourteenth day, but another week elapsed before the spirilla appeared in the circulating blood.

REVIEW OF AMERICAN CASE REPORTS FROM 1931 TO 1940

After a survey of the American literature recorded prior to 1931, Bayne-Jones[2] recognized seventy-five case reports as being typical of

the disease. To these may be added thirty-three recorded in the past ten years, as well as two older ones not included in the previous compilation,* a total of 110 since 1840. The new reports are summarized in Table I.

Geographic Distribution.—The disease has now been reported from twenty-eight states and the District of Columbia. The only large area from which no cases are included is the sparsely populated Rocky Mountain region (Fig. 1).

Fig. 1.—Distribution of ratbite fever in this country by states (1840-1940). Stippling indicates presence of disease.

Animal Vectors.—The rat continues as the chief source of human infection, but we call attention to two cases acquired from dogs,[29] two from cats,[25, 34] two from mice,[2, 28] and one from a laboratory rat.[6] In one instance,[34] contaminated soil appeared to be the source. Occurrence of the spirillum in laboratory mice has been stressed by Francis,[12] and the same fact has been noted here.

Clinical Course.—We know of few diseases in which the history is so universally repetitious as in ratbite fever. If allowance be made for concurrent pyogenic infection and instances of undiagnosed Haverhill fever, each case emphasizes the constancy of animal bite, latent period, recrudescence at the site of injury, periodic fever, and prompt response to arsenotherapy. We have been impressed by the severity of the anemia developing at times during the course of the disease, as well as by the marked debility which appears when treatment is not instituted promptly; one patient lost 50 pounds in the course of three months.[29] A macular rash has been noted in a majority of the more recent cases, some-

*These, one by Francis and one by Steiner, are included at the end of Table I.

TABLE I

RATBITE FEVER

TABULATION OF CASES REPORTED IN THE AMERICAN LITERATURE FROM 1931 TO 1940

NO.	AUTHOR	STATE	AGE (YR.)	SEX	ANIMAL	SEROLOGY	REMARKS
1	Orr[27]	Kentucky (prior to 1931)	5	M.	Rat	Wassermann + at 3 wk.; Kahn negative at 3 wk.	Typical case; incubation period, 3 wk.; rash present; isolation of organism not attempted; good response to neoarsphenamine
2	Jenkinson and Jordon[19]	Iowa (1930)	56	M.	Mouse	Wassermann negative, (?) time	Typical case; incubation period, 5 wk.; rash present locally; organisms not isolated; good response to neoarsphenamine
3	Mock and Morrow[25]	Illinois (1930)	43	M.	Cat	Wassermann not reported; Kahn ++ at 3 mo.	Typical case; incubation period undeterminable; rash seen on one occasion; organisms not isolated; good response to neoarsphenamine and none to mercury and iodides
4	Bloom[5]	Louisiana (prior to 1933)	2½	M.	Rat	Wassermann not reported; Kahn not reported	Typical case; incubation period, 4 wk.; rash present; organisms not isolated; good response to sulfarsphenamine
5	Van der Bogert[33]	New York (1933)	2½	M.	Rat	Wassermann negative at 3 wk.; Kahn not reported	Typical case; incubation period, 10 days; rash present; organisms not isolated; good response to sulfarsphenamine
6	Chapman and Chapman[7]	Texas (1933)	40	F.	Rat	Wassermann negative at 4 wk.	Typical case; incubation period, 3 wk.; rash present locally; isolation of organisms not attempted; good response to neoarsphenamine
7		Texas (1916)	?	F.	Rat	Wassermann not reported; Kahn not reported	Typical case; incubation period, 16 days; rash present; isolation of organisms not attempted; good response to neoarsphenamine

8	Caldwell and Templeton[6]	Wisconsin (1932)	28	F.	Rat	Wassermann ++++ at 3 wk.; Kahn not reported	Typical case from laboratory rat; incubation period, 5 days; rash present; organisms not isolated; fair response to arsenotherapy
9	James[18]	Tennessee (1932)	30	F.	Rat (white)	Wassermann negative at 4 wk.; Kahn negative at 4 wk.	Typical case; incubation period, 18 days; rash present; isolation of organisms not attempted; good response to neoarsphenamine and none to quinine
10	Ripley and Van Sant[29]	Illinois (1933)	26	M.	Dog	Wassermann negative at 9 wk.; Kahn ++++ at 9 wk.	Typical case acquired in dog surgery class; incubation period, 1 wk.; rash present; organisms isolated; good response to arsenotherapy
11		Illinois (1933)	22	M.	Dog	Wassermann negative at 8 wk.; Kahn ++++ at 8 wk.	Typical case from same source as No. 10; incubation period unknown; rash present; organisms isolated; good response to arsenotherapy
12	Edelman and Haber[9]	Ohio (1933)	5	M.	Rat	Wassermann +++ by 3 mo.; Kahn ++ at 4 wk.; Kahn ++++ at 8 wk.	Typical case; incubation period, 10 days; rash present; organisms not isolated; good response to sulfarsphenamine
13		Ohio (1933)	8	F.	Rat	Wassermann + at 2 mo.; Kahn ++++ at 2 mo.	History sketchy but fairly typical; rash present; isolation of organisms not attempted; no therapy at time of report
14		Ohio (1933)	?	F.	Rat	Wassermann ++ at 3 mo.; Kahn ++++ at 10 wk.	Typical case; incubation period, 6 wk.; rash not noted; organisms not isolated; good response to sulfarsphenamine
15	Koerber[20]	California (1934)	12	M.	Rat	Wassermann not reported; Kahn not reported	Typical case; incubation period, 3 wk.; rash absent; organisms isolated; good response to neoarsphenamine

TABLE I—CONT'D

NO.	AUTHOR	STATE	AGE (YR.)	SEX	ANIMAL	SEROLOGY	REMARKS
16	Marshall[23]	Kentucky (1933)	2	M.	Rat	Wassermann not reported; Kahn ++++	Typical case diagnosed in retrospect; rash not noted; incubation period, 3 to 4 wk.; treated with bismuth and mercury; results not known
17		Kentucky (1934)	2	M.	Rat	Wassermann ++++; Kahn ++++	Typical case; incubation period not stated; no rash mentioned; isolation of organisms not attempted; good response to stovarsol
18		Kentucky (1935)	8	M.	Rat	Wassermann not reported; Kahn not reported	Atypical as to rash and character of joint symptoms; might well have been streptothrix infection; no attempt to isolate organisms; treated with stovarsol
19	Woolley[36]	Massachusetts (1935)	6	M.	Rat	Wassermann negative at 5 wk.; Hinton negative at 3 wk.; Hinton positive at 5 wk.	Typical case; incubation period, 1 wk.; rash present; organisms recovered; good response to neoarsphenamine
20	Reitzel, et al.[28]	California (1934)	14	M.	Field mouse	Wassermann negative, 1 time; Kahn not reported	Typical case; incubation period, 12 days; rash present; organisms recovered; good response to neoarsphenamine
21	Walker[34]	Virginia (1934)	16	F.		Wassermann negative at 6 wk.; Kahn not reported	Typical case; apparently from wound contamination. Incubation period one week, rash present. Organisms isolated. Good response to neoarsphenamine
22		Virginia (1936)	50	F.	Cat	Wassermann negative at 2 mo.; Kahn not reported; Kline negative at 2 mo.	Typical case; incubation period, 2 wk.; rash present; organisms isolated; good response to neoarsphenamine

23	Garvin[15]	Ohio (prior to 1937)	7	M.	Rat	Wassermann not reported; Kahn not reported	Typical case; incubation period, 15 days; rash not mentioned; isolation of organisms not attempted; good response to neoarsphenamine; wound had been cauterized at time of injury with nitric acid
24	Bloch and Baldock[4]	Kentucky (1934)	3	F.	Rat	Wassermann ++ at 4 mo.; Kahn negative at 5 wk.	Typical case; incubation period, 4 wk.; rash present; organisms isolated; good response to neoarsphenamine
25	Leadingham*[22]	Georgia (prior to 1938)	7	M.	Rat	Wassermann negative at 3 mo.; Kahn not reported	Typical case; incubation period, 2 wk.; rash present; organisms isolated; good response to neoarsphenamine
26	Fisher[10]	W. Virginia (1938)	3	M.	Rat	Wassermann not reported; Kahn not reported	Complicated by pyogenic infection; rash present; isolation of organisms not attempted; good response to neoarsphenamine
27	Gilkey and Dennie[16]	Missouri (before 1938)	5	F.	Rat	Wassermann negative at 1 mo.; Kline ++++ at 1 mo.	Typical case; incubation period, 13 days; rash present; organisms not recovered; good response to neoarsphenamine
28		Missouri (before 1938)	5	F.	Rat	Wassermann not reported; Kahn not reported	Typical case; incubation period, 4 wk.; rash not mentioned; organisms not recovered; good response to neoarsphenamine
29		Missouri (1922)	5	F.	Rat	Wassermann ++++ at 10 wk.; Kahn not reported	Typical case; incubation period, 4 wk.; rash present; organisms seen in discharge from primary lesion; good response to arsphenamine

TABLE I—CONT'D

NO.	AUTHOR	STATE	AGE (YR.)	SEX	ANIMAL	SEROLOGY	REMARKS
30		Missouri (1935)	3	M.	Rat	Wassermann negative at 3 days; Kahn negative at 3 days	Typical case; incubation period not stated; rash not mentioned; organisms recovered; good response to neoarsphenamine
31	Hadley[17]	District of Columbia (1925)	42	M.	Rat	Wassermann negative, ? time; Kahn not reported	Typical case; incubation period, 10 days; rash present; isolation of organisms not attempted; good response to neoarspenamine
32	Woolley	Massachusetts (1938)	6	F.	Rat	Wassermann negative at 3 mo.; Hinton positive at 3 mo.	Typical case; incubation period, 2 wk.; rash present; organisms isolated; good response to neoarsphenamine
33		Oregon (1940)	6	M.	Rat	Wassermann not reported; Kahn ++++ at 6 wk.; Kline strongly positive at 6 wk.	Typical case; incubation period, 2 wk.; rash present; organisms recovered; good response to neoarsphenamine
	Steiner[32]	Connecticut (before 1930)	35	M.	Rat	Wassermann negative at 5 wk.; Kahn not reported	Typical case; incubation period, 4 to 5 wk.; rash present; organisms seen directly in blood smears; good response to neoarsphenamine
	Francis[11]	Virginia (before 1932)	6	M.		Wassermann not reported; Kahn not reported	Typical case; no definite history of rat bite but typical primary lesion; organisms recovered; good response to arsphenamine

*The first three cases in this report were tabulated earlier by Bayne-Jones. The fifth has not been included here because of semblance to pyogenic infection rather than spirillosis.

times only during peaks of fever and, occasionally, limited to the extremity upon which the bite occurred. Prominence of joint symptoms appears to be more characteristic of the Haverhill type, since it was not reported for a proved case of spirillosis, a point stressed by Allbritten and associates.[1]

Treatment.—Neoarsphenamine and sulfarsphenamine remain the drugs of choice, and both appear effective. Stovarsol has also proved of value.[23] No guide, other than clinical improvement, is available for determining the amount of therapy necessary for cure, but it would seem that eight to ten injections would err, if at all, on the side of safety. We found no record of the use of newer chemotherapeutic agents in proved cases, and no statement may be made regarding the value of local prophylactic measures. It is interesting that despite the growing literature on ratbite fever, a large portion of the cases was treated by incision of the primary lesion before the possibility of spirillosis was considered.

NOTES ON THE ISOLATION OF S. MINUS

S. minus has been recovered in this country from at least eighteen cases of ratbite fever (Table II), and several generalizations based on these experiences should be stressed. (1) During the active course of the disease the organisms are present in the chancroid primary lesion and the enlarged lymph nodes draining this area. They are to be found, at least intermittently, in the blood stream as well as in the macular skin lesions. (2) Little is known of their distribution in the body during the incubation period or after subsidence of acute symptoms. (3) *S. minus* cannot exist for long outside of the animal body and therefore cannot be obtained through the simple culture of blood. It can be recovered either directly from the host or through the medium of animal inoculation. (4) All laboratory animals are subject to infestation through natural channels, and it is paramount that animals used for the isolation of the spirillum be proved free from pre-existing infection by dark-field examination.

The direct examination of bodily fluids has given satisfactory results in a few hands, usually through the expression of lymph from the primary lesion and perusal in the dark field. The organisms have been identified once in preparations made directly from the patient's blood, but this is in contradistinction to the usual findings.*[32]

Inoculation of blood or lymph node juice into animals has proved of far greater value than the preceding method. Material from lymph nodes dependent to the primary lesion can be obtained by dissection or by puncture and aspiration. Blood is more likely to be satisfactory if it is withdrawn during one of the febrile episodes and injected immediately, without recourse to anticoagulants. The choice of animal is of secondary importance. Mice are small, frequently preinfested, and

*This has been reported also by Melanson in Canada.[24]

TABLE II

ISOLATION OF S. MINUS FROM RATBITE FEVER IN THE UNITED STATES

NO.	AUTHOR	DURATION OF DISEASE	SOURCE OF INOCULUM	ANIMAL USED	INCUBATION PERIOD	REMARKS
1	Shattuck and Theiler[30]	5 wk.	Blood	Guinea pigs White mice	15 days	Blood taken during a fall in temperature, citrated, and injected 45 min. later
2	Lanford[21]	6 wk.	Node juice	White mice	14 days	
3	Leadingham[22]	8 wk.	Blood	White mice	20 days	These 3 cases reported without further detail; no mention made of preliminary dark-field examination of mice
4		7 wk.	Blood	White mice	15 days	
5		12 wk.	Blood	White mice	20 days	
6	Bayne-Jones[3]	38 days	Skin macule	Guinea pig		Attempts to isolate organism by injection of blood unsuccessful
7	Walker[34]	Over 1 wk.	Blood	Guinea pigs	7 days	Represents the shortest incubation period with which we are familiar
8		Over 2 wk.	Blood	Guinea pigs	7 days	
9	Francis[11]	Over 2 mo.	Node juice (aspirated)	White rat		Inoculation of blood into white mice and guinea pigs unsuccessful
10	Koerber[20]	3 wk.	Node juice and blood	White rats Guinea pigs	Positive when first examined on 16th day	All animals injected with node juice were positive; only one receiving blood showed organisms

11	Gilkey and Dennie[16]	4 days	Node juice (aspirated)	White mice	13 days	Data not complete
12	Bloch and Baldock[4]	4 wk.	Blood	White mice	Between 10 and 20 days	Blood taken at height of fever and injected in 2 c.c. amounts
13	Reitzel et al.[28]	4 wk.	Node juice and blood	White mice	14 to 16 days	Blood and node juice injected into guinea pigs unsuccessful
14	Ripley and Van Sant[29]	2 mo.	Blood	White mice	11 days	Guinea pigs injected with blood were not successful; this strain was carried in mice, guinea pigs, and dogs after the initial isolation and increased virulence was demonstrated by serial transplants.
15		2 mo.	Blood	White mice	11 days	Experiments for Case 14 were repeated for this strain
16	Woolley[36]	5 wk.	Node juice	Guinea pigs	17 days	Attempts to infect guinea pigs with blood not successful
17	Woolley	3 mo.	Blood	Guinea pigs	17 days	Positive results obtained on three occasions
18		6 wk.	Node juice	Guinea pigs	21 days	This strain produced typical disease in guinea pigs but was not lethal

undergo no characteristic course when infected. Rats are large enough to accomodate an adequate inoculum but present the other disadvantages of mice. Guinea pigs, in our experience, have been quite satisfactory; they are large, rarely preinfested, and undergo a disease characterized by incubation period, local lesion, development of palpable nodes, alopecia, keratitis, and cachexia. The inoculum for guinea pigs and rats is best given subcutaneously and should not exceed 5 c.c. in amount. Mice may be injected intraperitoneally with 1 or 2 c.c. The length of time between inoculation and the appearance of spirilla in the blood stream is subject to variation with dosage and virulence of the strain. Seven days is the shortest period with which we are familiar, and in our cases we found seventeen days twice and three weeks once. Blood can be obtained from the tail in mice and rats and from the ear margin in guinea pigs. It should be examined under the dark stage and films prepared with Wright's stain for more leisurely study. Excellent photomicrographs are available[29] and are of assistance to one not familiar with the morphology of the organism. It should be stressed that a blood culture be made in every case of suspected ratbite fever as a means of ruling out the Haverhill type of infection.[1]

THE KAHN AND WASSERMANN REACTIONS DURING RATBITE FEVER

Bayne-Jones, after his review in 1931, concluded that there was no essential change in the Wassermann reaction during ratbite fever. It has been only during the last ten years that data have accumulated concerning the effect of the disease on the precipitin type of tests, as typified by those of Kahn and Hinton. The results by these methods are in direct contrast to those obtained by complement-fixing techniques (Wassermann and Kolmer). In fourteen cases Kahn or Hinton tests were made on blood samples drawn at least four weeks after the infection was acquired, and twelve of these showed some degree of modification. In several instances Wassermann tests were obtained on duplicate samples, and these were generally negative, in keeping with earlier observations. Sufficient evidence has accumulated to show that a change from negative reaction to positive begins to appear at the end of the fourth week, becomes stronger thereafter, and fades with the conclusion of adequate therapy.

This interesting relation* of positive precipitin test and absence of complement fixation appears to be of importance for four reasons: (1) As an aid in the diagnosis of ratbite fever; (2) as a guide to treatment and as a criterion of cure in ratbite fever; (3) in establishing ratbite fever as another variable in the diagnosis of syphilis by laboratory measures; and (4) as a factor to be considered in the appraisal of serologic findings during the use of the spirillum in the treatment of syphilis of the central nervous system. We feel that the results at the

*No explanation is offered for this phenomenon, but it is probably quantitative and a reflection of the greater sensitivity, and as a corollary, the lesser specificity, of the precipitin methods.

present time justify a certain amount of confidence in the diagnostic significance of a positive precipitin test, but that its value in governing therapy must be confirmed by future observations.

SUMMARY AND CONCLUSIONS

Two cases of ratbite fever are reported.

A review of American case reports since the last compilation in 1931 adds thirty-three instances of infection and brings the total reported for this country to 110.

S. minus has been isolated from at least eighteen of these cases, and the technique is discussed. Most dependable results are obtained by the use of lymph node emulsion injected into guinea pigs.

The precipitin type of serologic test, such as that of Kahn or Hinton, is positive in about 90 per cent of cases by the end of the fourth week, while the Wassermann reaction is usually negative. The possible value of these findings is discussed.

The first case reported is from the files of the Infants' Hospital, Boston. The second is included through the kindness of Dr. L. Howard Smith, Portland.

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3181 S. W. MARQUAM HILL ROAD

BERIBERI IN A MALE CHILD TWO AND ONE-HALF YEARS OF AGE

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CASE REPORT

THE early history of the patient revealed that because of anorexia and habit vomiting the food intake for several months consisted largely of milled white cereal which was given frequently and in large portions. During the preceding four weeks there had been a loss of 4 pounds in weight. Signs indicating an unusual illness had been observed for two weeks, unusual in that the only symptoms related to the objective and were in no way of a constitutional nature. The boy preferred to sit quietly, undisturbed; this attracted the parents' attention as the patient had always been of an exceedingly active type. In addition to this change in conduct, manipulation was accompanied by crying and was strongly resisted. Bathing and the use of the toilet in the usual position soon became impossible. In walking the posture had changed, the trunk being held in a rigid fashion, and all voluntary movement ceased.

Examination.—All the organs including the heart and lungs were negative; the blood and urine were normal. The boy evidenced great pain during the necessary manipulation of the examination and cried bitterly. There was entire absence of flexibility of the spinal column; the pain and tenderness seemed to be located chiefly in the thoracic, abdominal, and lumbar muscles. In the erect position the trunk was held rigid in a modified opisthotonos fashion (Fig. 1). In ascending stairs he rested the right hand on the balustrade and pulled; he pushed with the left hand on the left knee in order to ascend. In the supine position it was impossible for him to arise; on hands and knees he sought assistance which was supplied by an article of office furniture (Fig. 2), presenting an ideal symptom complex of pseudo-muscular dystrophy with an acute peripheral polyneuritis. Mentally he was normal for his age, a bit precocious, and highly combative.

Diagnosis.—Avitaminosis, beriberi type.

Management.—He was given three meals daily of milk, meat, eggs, vegetables, and fruits, with nothing but water between meals. Medication consisted of 15 mg. Mead's oleum percomorph 50 per cent, and 50 mg. nicotinic acid in divided doses daily, reduced after three days to 12.5 mg. because of a skin eruption.

Eleven days after the initial visit a dramatic improvement was apparent. He showed no resistance to manipulation and no objection to the bath or toilet, ascended stairs in a normal fashion, and climbed on and off a bench unaided. In Fig. 3 the child is shown in a crouching position with the spinal column flexed, picking up a penny from the floor.

His disposition and mental reactions were usual for a child who had been spoiled for two and one-half years.

One Year After Initial Visit.—During this period he had been well in all respects, nutritionally and otherwise, and had grown 3⅘ inches in height and gained 10 pounds in weight. Fig. 4 is inserted to demonstrate an entire absence of symptoms of muscular dystrophy.

In a private contribution Dr. Gilbert Dalldorf[1] wrote me as follows: "I do not know of published instances in which nicotinic acid has been

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Fig. 1.—When this photograph was made, it was impossible for the patient to stand unaided. Moderate degree of lordosis present.

Fig. 2.

Fig. 3.

Fig. 2.—Patient making effort to assume upright position.
Fig. 3.—After eleven days of treatment, the patient displayed perfect flexibility in picking up a penny from the floor.

Fig. 4.—May 2, 1941. Patient at age of 3 years, 6 months, showing normal flexibility. Weight, 36 pounds; height 38.8 inches.

used. Therefore I am very glad to have learned of your experience and to see it recorded. I think we should be willing to accept the possibility that large doses of pure vitamins may have an immediate pharmacological action distinct from the quenching of a deficiency. I believe the action of B_6 in Parkinson's disease may be of this order and that some of the reported effects of nicotinic acid also. This is an important distinction for us to keep in mind in interpreting your experience."

Nicotinic acid was given instead of thiamin because I had found it particularly potent in neuritic disorders in children.

Interesting and unexpected was the satisfactory physical condition of the child. Other than the neuritic manifestations, the physical examination was largely negative.

This feature is referred to by Mouriquand[2] as follows: "Humans may present the picture of good or relatively good health for a long time on a diet deficient in accessory factors and ill-balanced in composition, during which no clinical signs call attention to any ever so mild disorder because of this nutritional deficiency. They are looked upon as healthy until a precipitant factor, alimentary, physiological or of infectious origin exteriorizes as it were, their hidden ill balance and turns this asymptomatic into a symptomatic state."

A timely editorial in a recent number of the *Journal of the American Medical Association* calls attention to the recentness of vitamin therapy and suggests that clinical effects on the human being cannot necessarily be evaluated by means of the laboratory animal. A question naturally arises as to what bearing persistent avitaminosis B might have as an etiologic factor in pseudohypertrophic muscular dystrophy.

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NONHEMOLYTIC STREPTOCOCCUS OMPHALITIS, PAROTITIS, AND MENINGITIS IN A PREMATURE INFANT

Report of a Case

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SINCE the introduction of the sulfonamide group of drugs into clinical medicine, many remarkable chemotherapeutic cures have been reported. The following is a report of a prematurely born infant who had a nonhemolytic streptococcus sepsis. The case is of interest because of the unusual recovery from three serious complications: omphalitis, parotitis, and meningitis.

REPORT OF CASE

E. A. L., a white male infant, was delivered on Dec. 29, 1940, three weeks before term and thirty hours after an emergency hemorrhoidectomy on the mother for large gangrenous hemorrhoids. Weight at birth was 5 pounds, 3 ounces. The infant was cyanotic and drowsy but responded to resuscitation. He was placed in an incubator and after twenty-four hours was started on Olac feedings. On the fourth day of life, the infant developed a temperature of 102.4° F. with no other signs of infection. The cord stump was still attached and appeared normal. The temperature returned to normal after a clysis of 50 c.c. of saline.

On the seventh day of life, several hours after the umbilical cord fell off, a yellow purulent drainage was noticed on the dressing. Culture of this revealed a nonhemolytic, nonpigment-producing, short chain streptococcus. The area surrounding the umbilicus was normal, the abdomen was soft, and there was no fever. The infant took his feedings well and gained weight. Ethyl alcohol followed by 10 per cent sulfathiazole ointment was applied locally twice daily (Fig. 1). After four days, the drainage stopped completely, and treatment was discontinued. The baby was removed from the incubator on the thirteenth day of life, at which time he weighed 5 pounds, 7 ounces. On the sixteenth day of life, the umbilicus developed a dry redness and induration. Wet boric acid packs were applied, and gr. ¼ sulfathiazole was given orally every four hours (Fig. 1). The umbilicus seemed healed after thirty-six hours, but the sulfathiazole was continued for another thirty-six hours. The infant's course during the next twenty days was very satisfactory. He took his feedings well and gained from 5 pounds, 11 ounces, to 7 pounds, 4 ounces. His temperature and blood findings were normal.

On the thirty-ninth day of life, his temperature rose to 100.4° F. He developed a yellowish mucopurulent nasal discharge and signs of an upper respiratory infection. He became very irritable and cried as if in pain. Abdominal distention and a progressive and marked swelling of the lids of both eyes and of both parotid and submaxillary glands developed. There was some redness around Stensen's ducts, but no material could be expressed by pressure on the parotid glands. The face, scalp, and neck became markedly edematous. The thick mucopurulent nasal discharge revealed a nonhemolytic, nonpigment-producing, short chain streptococcus on culture. The extreme abdominal distention was not relieved by enemas. Respirations were 80 to 100 per minute. The heart sounds were of poor quality, and the rate was too rapid to record. Examination of the blood showed 1,570,000 red blood cells and 38 per cent hemoglobin. The infant seemed to be failing rapidly. He

From the Menorah Hospital.

was given 50 c.c. of the father's whole blood into the ankle vein with some clinical improvement. One and one-half grains of sulfathiazole were given every four hours. His weight was 7 pounds, 4 ounces (Fig. 2). The next day the infant appeared improved, although the temperature was now 102.6° F. He was given 20 c.c. more of whole blood intravenously. Sulfathiazole dosage was reduced from 1½ gr. to 1 gr. after forty-eight hours and continued for the next four days. On the fifth day after the onset of the parotitis, the temperature was normal, and the swelling of the head, neck, eyelids, and parotid and submaxillary glands had subsided almost completely. The infant seemed to be entirely well, and sulfathiazole was discontinued seventy-two hours later.

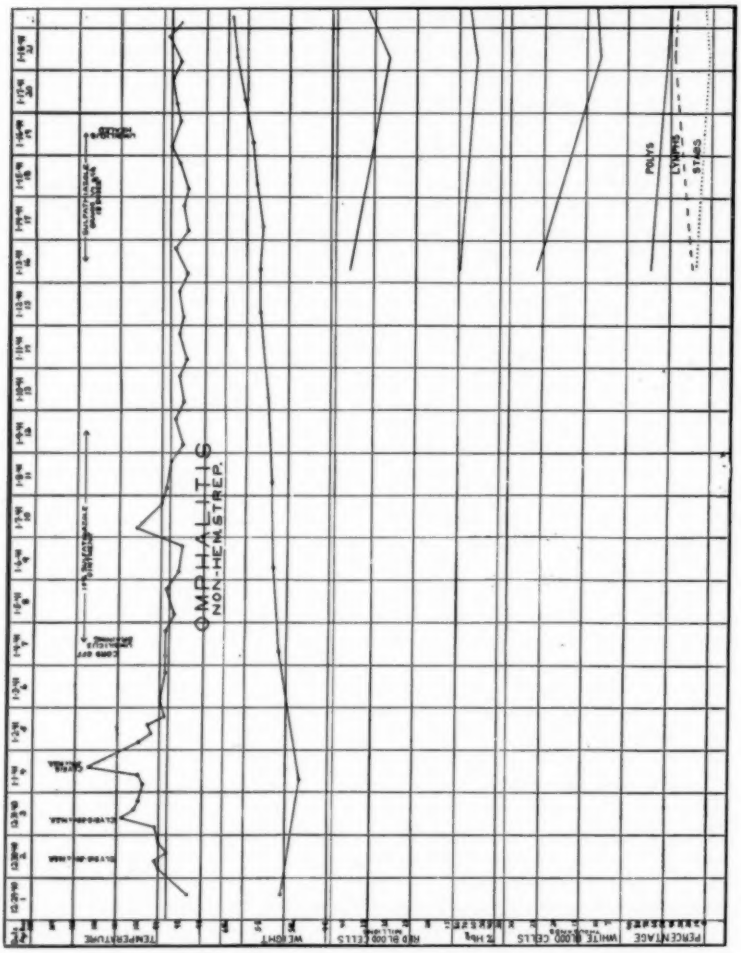

Fig. 1.

On the forty-eighth day of life, four days after the subsidence of the parotitis, the temperature rose slightly, and a mucous nasal discharge was again noticed. Three grains of sulfathiazole were given initially, followed by 1½ gr. every four

hours. After twelve hours, the infant became increasingly irritable, and the temperature rose to 103.4° F. He vomited a few times after feedings. The cry was one of severe pain but not cephalic in character. There was no bulging of the fontanel. Kernig and Brudzinski signs were absent. Slight jarring of the bassinet or noises caused the infant to react suddenly with a positive Moro reflex and to

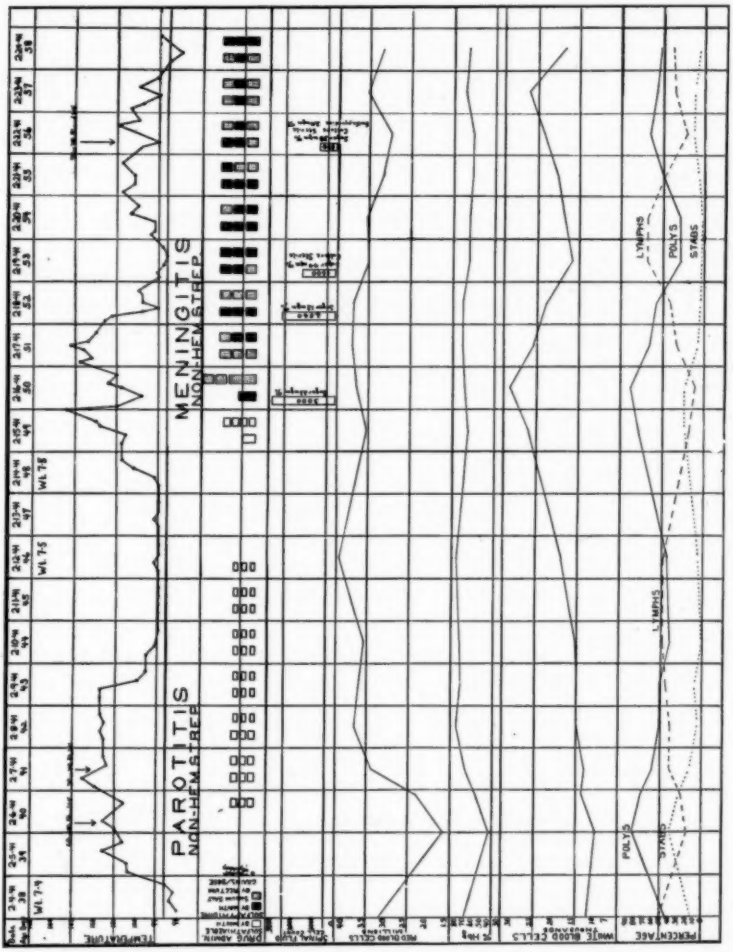

Fig. 2.

cry as if in severe pain. A spinal puncture, thirty-six hours after the onset, revealed a cloudy gray fluid under some increased pressure. Cell count was 3,000 with 93 per cent polymorphonuclears; sugar, 23 mg. per cent. Colloidal gold test showed a meningitic curve. Culture was contaminated. Because of vomiting, he was given the sodium salt of sulfapyridine by rectum, as described by Hartmann and Barnett. A 2 per cent solution of sodium sulfapyridine in distilled water was used. The initial dose was 20 c.c. (6.2 gr.), followed by 8 c.c. (2.5 gr.) every four hours.

This solution was made up fresh every day. After thirty-two hours, it was decided to resort to oral medication because of rectal irritation manifested by slight diarrhea. This consisted of 2½ gr. of sulfapyridine every four hours. If this was not retained, the rectal medication was given. The infant showed gradual signs of improvement under this course of treatment. Parenteral fluids were unnecessary during the illness, because water balance was maintained by oral administration. Nembutal, ½ gr. by rectum, was used for sedation during the early part of the meningitis.

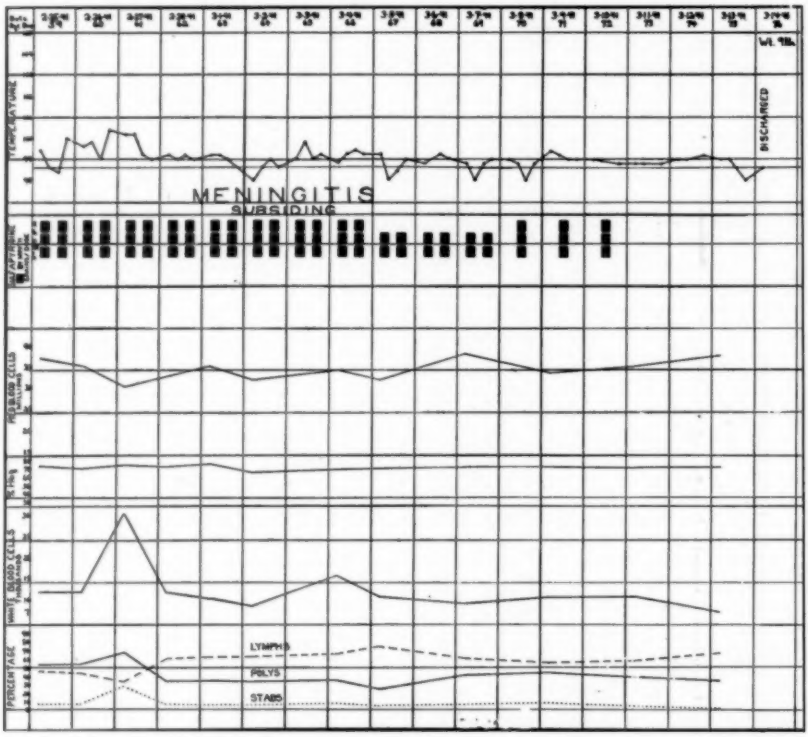

Fig. 3.

Spinal puncture on the fifth day revealed a less cloudy fluid under the same increased pressure. Cell count was 2,560 with 90 per cent polymorphonuclears; sugar, 12 mg. per cent. Culture showed nonhemolytic, nonpigment-producing, short chain streptococcus. This was the same organism cultured earlier from the omphalitis and parotitis and from the pelvic abscesses of the mother who was by this time critically ill. Cisternal puncture on the sixth day showed a less cloudy fluid still under increased pressure. Cell count was 1,600 with polymorphonuclears predominant; sugar, 44 mg. per cent. The culture was sterile. Cisternal puncture on the ninth day of the illness revealed a much less cloudy fluid with decreased pressure. Cell count was 800 with a smaller percentage of polymorphonuclears; sugar, 38 mg. per cent; culture, sterile. Spinal fluid sulfapyridine was 2.4 mg. per cent.

Because of an increasing anemia, 50 c.c. of whole blood were given into the ankle vein on the ninth day of the meningitis. By the twelfth day, the infant was able to take the sulfapyridine entirely by mouth. On the thirteenth and fourteenth days of the illness, he developed signs of an upper respiratory infection with nasal discharge, a temperature of 100.4° F., and an increase in white blood cell count to 30,600 with 87 per cent polymorphonuclears and 25 per cent stabs. This subsided after twenty-four hours (Fig. 3). Sulfapyridine medication by mouth was continued in 2½ gr. doses every four hours until the twentieth day of illness, which was six days after the temperature had returned to normal. The dose was gradually decreased and then discontinued six days later.

The urine was negative throughout the illnesses.

The infant was discharged entirely cured on the seventy-sixth day of life, weighing 9 pounds. There was no evidence of any residual effects from his illnesses. When last examined at the age of 4 months, he was progressing normally and weighed 12 pounds 2 ounces.

SUMMARY AND CONCLUSIONS

A successfully treated case of nonhemolytic streptococcus sepsis with omphalitis, parotitis, and meningitis in a premature infant is reported. The source of the infection was the mother, and the portal of entry was the umbilical cord. The mother had a very stormy post-partum course and developed multiple pelvic abscesses from which the same streptococci were cultured.

The total amount of sulfathiazole and sulfapyridine which the baby received during his illnesses was 363.2 gr., or 24.2 Gm. During the twenty-three days of treatment for the meningitis, he received a total of 61.2 gr. of sodium sulfapyridine and 246.5 gr. of sulfapyridine. At no time during the medication was there any evidence of toxicity from the drugs.

This case demonstrates the superiority of sulfapyridine over sulfathiazole in the treatment of newborn infants with severe infections other than those caused by staphylococci. The greater diffusibility of sulfapyridine into the spinal fluid and the increased meningeal permeability in the newborn infant make it the drug of choice.

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RECOVERY FROM TWO ATTACKS OF MENINGITIS CAUSED BY DIFFERENT ORGANISMS

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RECOVERY from one attack of any type of purulent meningitis has become commonplace since the advent of the sulfonamides, but recovery from two attacks, separated by a wide time interval and each caused by a different organism, is unique, although recurrent pneumococcic meningitis has been reported.[1] As more patients are cured by chemotherapy, multiple attacks may become more frequent. In 1938 our patient recovered from streptococcic meningitis on sulfanilamide therapy and three years later was cured of pneumococcic meningitis by sulfapyridine.

CASE REPORT

First Admission.—On Jan. 1, 1938, J. B., a 7-year-old white boy, entered Duke Hospital, having been unconscious for twelve hours before admission. One sister had died of meningitis in 1920. His past history was noncontributory. The day before admission the patient appeared ill, refused meals, and complained of frontal headache; soon he began to vomit, later developed high fever and delirium, and for the twelve hours prior to admission to the hospital was unconscious.

Physical examination revealed temperature, 38.3° C. (101.1° F.); pulse, 120; respirations, 22. The patient was an acutely ill child who resisted all passive motion. There was a herpetic rash on his chin. The eyes were normal, the mouth was dry and dirty, and the tonsils and pharynx were hyperemic. The neck was stiff and held in opisthotonus. The heart, lungs, abdomen, and neurologic examination were essentially normal. The Kernig and Brudzinski signs were positive.

Accessory clinical findings were hemoglobin, 84 per cent; red blood cell count, 4,100,000; white blood cell count, 34,000. Urinalysis, tuberculin and Wassermann tests, and stools were negative. The spinal fluid was purulent and under increased pressure. The Pandy test was three plus, and the cell count was 1,800, mainly polymorphonuclear neutrophiles. Stained smears revealed gram-positive cocci which on culture were beta hemolytic streptococci.

Hospital Course.—Because of the cloudy spinal fluid, one dose of antimeningococcus serum was given intrathecally, and sulfanilamide was started, 0.9 Gm. every six hours, and increased on the third hospital day to 0.9 Gm. every four hours. The blood sulfanilamide levels ranged from 7.5 to 15 mg. per cent, and the spinal fluid levels, from 3.5 to 10 mg. per cent. For the first three days the spinal fluid culture was positive for beta hemolytic streptococci but thereafter was sterile. The temperature fell to normal on the sixth hospital day. Sulfanilamide was discontinued on the twelfth hospital day, and the patient was discharged seven days later.

Interval Note.—Since discharge on Jan. 9, 1938, the patient had been well except for a brief illness six months before the second admission. This illness was said to be characterized by fever, projectile vomiting, stiff neck, severe headache, mental confusion, and lethargy. Lumbar puncture at that time showed spinal fluid to be under increased pressure, with a cell count of about ten lymphocytes per cubic millimeter and a negative Pandy test. The diagnosis at that time was said to be "acute lymphocytic meningitis." This illness lasted about two weeks.

Second Admission.—On March 2, 1941, this patient, who was now 10 years of age, returned to Duke Hospital complaining of "spinal meningitis." Three weeks before

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admission he had had a severe cold, which cleared up except for a mild cough. Two days before this admission he awoke with a severe frontal headache and soon began to have projectile vomiting and pain in his neck. Subsequently his temperature rose, and he became drowsy.

Physical examination showed temperature, 39.9° C. (103.8° F.); pulse 120; respirations, 24; blood pressure, 112/70. The patient was a flushed, rather obese, white boy 10 years of age, appearing acutely ill. There was slight, bilateral papilledema. There was a profuse nasal discharge. The tongue was dry and coated, and the tonsils and pharynx were inflamed. The neck was very stiff and painful on any motion. The Kernig and Brudzinski signs were strongly positive bilaterally. The remainder of the physical examination was essentially normal.

Accessory clinical findings were hemoglobin, 13.8 Gm. (86 per cent); red blood cell count, 5,500,000; white blood cell count, 24,500. The differential white blood cell count was normal except for a moderate increase in immature polymorphonuclear neutrophiles. The Wassermann test was negative. The urine showed a one plus albumin and acetone and an occasional white blood cell. The spinal fluid was cloudy but was under normal pressure; the Pandy test was strongly positive; the cell count was 1,790, mostly polymorphonuclear neutrophiles. Stained smears revealed gram-positive diplococci which on culture proved to be pneumococci. Attemps at typing the cultured organisms were unsuccessful. X-rays of the patient's sinuses disclosed a dense mass involving the right maxillary antrum and apparently the ethmoid and sphenoid sinuses. This was thought to be an osteoma, but a proliferative periostitis could not be ruled out.

Hospital Course.—The patient was given 2 Gm. of sodium sulfapyridine intravenously and then received 0.75 Gm. of sulfapyridine by mouth every four hours. This dosage was increased to 1 Gm. every four hours the following day and again to 1.5 Gm. every four hours on the sixth hospital day. Daily intravenous doses of 2 to 3 Gm. of sodium sulfapyridine were given also for the first nine days of the patient's stay in the hospital. The blood sulfapyridine levels ranged from 3.5 to 6.3 mg. per cent. The patient's improvement was immediate and dramatic, the temperature falling to normal on the third hospital day and remaining below 38° C. (100.4° F.) until discharge, and the signs of meningeal irritation disappearing by the sixth hospital day. On his second hospital day the patient developed severe herpes simplex in and about his mouth and on his chin, but this cleared rapidly after large doses of thiamin chloride were given. No toxic reactions to the chemotherapy occurred except a moderate fall in hemoglobin and the white blood cell count, and, while he was receiving intravenous sodium sulfapyridine, rather severe nausea and vomiting. Chemotherapy was stopped on the patient's fourteenth day in the hospital, and he was discharged four days later with instructions to return at a later date for exploration of the antrum, in view of the possible role that the abnormality of the sinuses might play in increasing the patient's susceptibility to meningeal infections.

SUMMARY

This patient had two attacks of purulent meningitis, separated by a three-year interval of good health and caused by two different organisms. The first attack, due to a beta hemolytic streptococcic organism, was cured with sulfanilamide therapy; the second, due to the pneumococcus, was cured with sulfapyridine.

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PARENTAL EDUCATION IN MENTAL HYGIENE

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STATEMENTS to the effect that there are very few problem children but that there are a great many problem parents can be found in the writings of almost every author interested in the behavior disorders of children. While little consideration has been given to the training of individuals for parenthood, the development of agencies to correct personality difficulties in children is steadily increasing. We are realizing that we would rather have our child "be a reasonable, lovable human being," as Sweet[1] puts it, "who can live happily with his fellows, even though his health isn't altogether perfect, than to be the healthiest 'animal' in creation."

We now have a number of child guidance clinics throughout the country for the scientific handling of problem children. Hardcastle[2] states that the movement to form clinics of this sort originated in 1909 when Dr. W. Healy founded the Juvenile Psychopathic Institute of Chicago in connection with the juvenile court there. In 1912 the Boston Psychopathic Hospital established a special clinic for children. A year later the Henry Phipps Psychiatric Clinic in Baltimore founded a similar service. In 1922, after the National Committee for Mental Hygiene had surveyed a number of schools and had found the methods of handling problem children altogether inadequate, the Commonwealth Fund financed several child guidance clinics in many of our larger cities.

Now that these agencies have been established, they have been reporting information which I feel has not been sufficiently emphasized in the literature. Field[3] examined the mothers of twenty-five consecutive children diagnosed as cases of primary behavior disorders in the New York State Psychiatric Institute between July 1, 1935, and July 1, 1937. "Not a single mother was a well integrated individual," she writes, "discharging her duties of a wife and mother in an adult fashion."

Field further pointed out that twenty-three out of these twenty-five children were rejected by one or both parents. Figgs[4] defines a rejecting parent as one "whose behavior towards her child is such that she consciously or unconsciously has a desire to be free from the child and considers it a burden." Eighteen of the twenty-five mothers examined by Field showed underlove combined with overcontrol of the child.

Witmer,[5] of the Smith College for social work, studying parental behavior as an index to the probable outcome of treatment in a child guidance clinic, concludes, "The mother is the key person by whose behavior the outcome of treatment might be predicted."

Witmer found that for children whose mothers showed extreme lack of affection, treatment by a modern child guidance clinic was a total failure

in over 90 per cent of the cases. In other words, this clinic found that a rejecting attitude in the mother will almost always permanently crimp a young personality, providing the latter develops a behavior problem. There is no way of estimating what proportion of the children of rejecting mothers develops nervous difficulties. Obviously the ones escaping disorders are not brought to a clinic. Since the work of Freud,[6] we have known the importance of early childhood maladjustments in the formation of the neuroses of adult life. In a child the parental attitude of rejection has a much more sinister aftereffect than physical suffering.

On the other hand, conscientious parents far too often lean over backward in their attempt to allow their children to grow up free and unhampered. They take their children's "I don't love you any more" too seriously and become fearful lest any sort of discipline will permanently damage their child's mental growth. The child then, never being crossed in his formative years, grows up a victim of his selfish whims. This oversolicitous attitude of parents, this fear of thwarting the child, is quite as pernicious as its domineering, rejecting opposite. Clinical data bear this out. Witmer further found that if the child was overprotected to the extent that, after growing up with selfish tendencies, he irked the mother to the habit of nagging, his chances of being helped by a clinic were practically nil. Out of nine children of this group, all nine remained uninfluenced by clinic treatment.

Data such as these impress on us the tremendous power that parents wield over their children. With this power comes the responsibility to train them into healthy, useful adults, free from miserable complexes arising from a mishandled childhood. Parents must be trained for their job. In their care is entrusted the most extraordinary mechanism known—a developing human personality. We must realize that the training of human beings can be no longer left to chance. We must become skilled if we are to have the next generation disciplined and useful.

We should think of unhealthy adult attitudes in the same way that we think of contagious disease. Young natures are perishable and are capable of being lacerated, infected, and even permanently damaged as certainly as is living flesh.

Our handling of the problem of behavior disorders as well as the common neuroses is now, we hope, curative, but not as yet preventive. It has advanced about as far as typhoid fever had before the epidemiologists and sanitary engineers contributed their splendid work. If we would relieve mental suffering on a wholesale scale, we should attempt various methods of mass educating the parents of today and require training for parenthood in our schools to ensure healthy home groups of tomorrow.

We must go to the recognized authorities in child guidance for our basic information; then pool this combined wisdom and distribute it just as widely as possible. Such men as Drs. D. H. Thom, C. Anderson

Aldrich, Karl Menninger, Clifford Sweet, and others know much more than the rest of us about managing the formative years of our children in an understanding way. These men could plan a course to be used in our high schools which would give future parents a technical knowledge that we do not have.

How could we best distribute authoritative information widely to the present group of parents? Can we work through the medical profession, making the general practitioner responsible for dispensing mental health principles in his community? In 1931, Ziegler[7] set out to test the enthusiasm of the profession as a whole for mental hygiene. Of the ninety-five physicians whom he interviewed, only twenty-eight expressed much interest in nervous conditions. A mere twelve said that they were very much interested in mental disorders. To a questionnaire that Ziegler sent out, forty-six out of the ninety-nine who replied answered that they knew nothing of mental hygiene. There were forty-eight who reported knowing very little and only five who felt themselves to be well informed. In view of reports like this, a widespread lecture series system of parental education is not feasible, because our medical men themselves lack training.

As an alternative, I wish to suggest the creation of a series of motion-picture shorts, written jointly by the proper child guidance experts and experienced movie script writers. The common situations that arise in family life are sufficiently stereotyped that they lend themselves easily to dramatization. The sibling rivalry situation, refusal of food, stealing, etc., could be presented in the form of short movies, showing the common mistakes that are made and demonstrating the correct technique of the wise parent. Physicians could give the facts and the treatment contained in each movie, and then the script writers could mold them into very instructive and entertaining movie short subjects.

In the motion picture we have a vast distribution medium that would come nearer than any other to reaching everyone. It has been used for similar purposes before. The present "Crime Doesn't Pay" series and the "Birth of a Baby" in the spring of 1938 are examples. Persons who went to the latter production have a firm idea now as to the proper procedures in prenatal care and home delivery technique. Plass,[8] Adair, McCord, and Williams, who were the medical advisors of this movie, are enthusiastic in their conviction that the movie can have real lay educational value in the fields of hygiene and preventive medicine.

The distribution of our scientific advances to the whole mass of people is lacking woefully in breadth and depth, as Colver[9] has pointed out, and is due to the reluctance of the medical profession to take the public into its confidence. There is too wide a gulf between the specialist and the layman. The latter must have the help of the former if he is going to train his children to adjust themselves to this increasingly complex world. The fact that in 1938 there were approximately 600,000 beds

for nervous and mental patients as compared to 425,000 for general hospital care shows the enormity of the problem and the need for preventive work in this field. We must begin by teaching large masses of people how to rear their children wisely. We can distribute widely the combined experience and training of our best minds if we will just put forth a cooperative effort to bring this about.

SUMMARY

Although little consideration has been given to the training of individuals for parenthood, the development of agencies for child guidance is steadily increasing.

Attitudes of untrained parents have the power to permanently cripple the personalities of children.

A high school course in parenthood, written by child specialists, is advocated.

A plan to create motion picture short subjects under the supervision of child experts for the mass education of present-day parents is urged.

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TUBERCULIN PATCH TEST (VOLLMER) ON B C G VACCINATED AND CONTROL CHILDREN

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A NUMBER of studies have been published recently on a tuberculin patch test as described by Vollmer.[1] These studies have been concerned, for the most part, with a comparison between the patch and intradermal methods of administering tuberculin to children of a known tuberculous process, active or inactive. It is agreed generally that such processes are associated with a degree of tuberculin activity usually higher than that following B C G vaccination. Consequently a comparative study in B C G vaccinated children seemed to offer a reasonably crucial trial of the efficiency of the patch test.

The children concerned in the present study, half of whom were vaccinated with B C G at 4 to 7 days of age,[2] have been followed from birth by semiannual clinic visits. The immediate members of the family were examined roentgenologically by chest plate before the birth of the child. The subjects of this report were all delivered at Cook County Hospital and consequently came from more or less the same economic strata, the race distribution being approximately 63 per cent colored and 37 per cent white. The immediate family environment was nontuberculous. However, the general milieu of the great majority of the children shows a high incidence of tuberculosis based upon the recently reported morbidity and mortality statistics indicated by census districts of the city of Chicago.[3]

The follow-up studies of these children included among other things semiannual tuberculin tests. These are, of course, necessary for the determination of infection among the control children on the one hand and to estimate the duration of the allergic response of the vaccinated children on the other. Statistics concerning this particular phase of the problem are being published elsewhere.[2]

The routine established was to perform a Mantoux test on the right forearm using 0.1 c.c. of old tuberculin in concentration varying from 1:1,000 to 1:100. At the same time a patch test was applied to the interscapular region in the horizontal plane. The Mantoux tests were read in forty-eight hours and the patches removed. Two days later, or ninety-six hours from the time of application, the children were again seen and the patch test read.

In Table I are summarized the results of this study. Comparisons were made between the patch test and Mantoux test done with different dilutions of old tuberculin. The dilution of tuberculin was determined

From the Tice Laboratories, Research Department, Chicago Municipal Tuberculosis Sanitarium, and from the Department of Pathology, Bacteriology, and Public Health, University of Illinois College of Medicine.
The Vollmer patches were kindly supplied by the Lederle Laboratories.

TABLE I

COMPARISON OF PATCH AND MANTOUX TESTS

NO. TESTED	B C G VACCINATED 101			CONTROLS 106			TOTAL 207			PERCENTAGE AGREEMENT
TYPE OF TEST	MANTOUX O. T. DIL.	MANTOUX NO. POS.	PATCH NO. POS.	MANTOUX O. T. DIL.	MANTOUX NO. POS.	PATCH NO. POS.	MANTOUX O. T. DIL.	MANTOUX NO. POS.	PATCH NO. POS.	
	1:1,000	9	7	1:1,000	0	0	1:1,000	9	7	77.7
	1:500	25	24	1:500	0	0	1:500	25	24	96.0
	1:200	53	50	1:200	6	5	1:200	59	55	93.2
	1:100	10	7	1:100	1	1	1:100	11	8	72.7
	Rpt.* Req.	3	1	Rpt. Req.	1	1	Rpt. Req.	4	2	50.0
Mantoux and Patch pos.	89			7			96			
Mantoux pos. Patch neg.	11			1			12			88.8
Mantoux and Patch neg.	1			98†			99			
Mantoux neg. Patch pos.	0			0			0			100.0

*Rpt. Req. = repeat required; indicates that the Mantoux test was at first negative, but when repeated with a higher concentration in the other arm immediately after reading first test, it was positive.

†Of these 98 cases, 32 were tested with 1:1,000, 20 were tested with 1:500, 39 were tested with 1:200, and 7 were tested with 1:100.

by the age of the child. Children under 7 months of age were injected with a 1:1,000 dilution, those from 8 to 14 months of age with a 1:500 dilution, those from 15 months to 3 years with a 1:200 dilution, and those 3 years and over with a 1:100 dilution. In all cases except the four indicated in the "Repeat Required" space only one test was performed. The use of these dilutions was dictated by convenience since it is obvious that the older a child is, the longer is the interval since vaccination. It has been shown by other authors[4] that sensitivity to tuberculin following B C G vaccination reaches a certain height, then falls off slowly. Therefore, to obviate the use of more than one Mantoux test, the higher concentrations were used in the older age groups.

It was unfortunate that in the 207 unselected consecutive children tested, only nine of those vaccinated were injected with the 1:1,000 dilution of old tuberculin. However, the falling percentages of agreement indicated in the last column correspond to the falling dilutions of tuberculin. The implication seems to be clear that the patch test is positive in the greatest percentage in individuals of high sensitivity. Although the numbers are small there is even a good agreement in individuals of low sensitivity. In the four patients requiring repeated Mantoux tests, it is noteworthy that the patch was positive. In one of these patients it was necessary to do three Mantoux tests with increasing concentrations of old tuberculin before a positive was obtained. However, in two other such instances the patch was negative although the second Mantoux was positive.

Further analysis of the figures in Table I shows (1) that in cases in which the Mantoux test was positive, the patch was positive in 88.8 per cent of the cases; (2) that in cases in which the Mantoux was negative, the patch was negative in 100 per cent. Combination of the two sets of individuals indicates an agreement between the patch and Mantoux in 94.2 per cent of the 207 cases studied.

An analysis of the 12 cases in which disagreement was manifest between the patch and Mantoux as to age, sex, and race, yields no significant data. Five were under and seven were over 1 year of age; 9 were males and 3 were females; and 9 were colored and 3 were white. The race distribution is that of the entire group and the apparent preponderance of males is not statistically significant. It seems reasonable to comment that within the limits of this study, age, sex, and race play no role in reactivity to tuberculin by the patch test.

Since we had the opportunity to observe the reaction to the tuberculin patch test at forty-eight hours, we thought it would be interesting to compare reactions at forty-eight hours and at ninety-six hours. This comparison was recorded in 114 cases, and the results are summarized in Table II. It is seen that in six instances the patch was mildly positive

TABLE II

COMPARISON OF READINGS AT 48 AND 96 HOURS

Patch positive at 48 and 96	41
Patch negative at 48 and 96	55
Patch positive at 48	6*
Patch negative at 96	
Patch negative at 48	12
Patch positive at 96	

*All mild, ranging from one vesicle to ten vesicles on one patch.

in forty-eight hours and negative in ninety-six hours. In two of these children the Mantoux was positive. What theoretical significance this observation may have is problematical. From the practical point of view it obviously carries little value because a Mantoux would give one the true character of the reaction of the individual. In twelve instances the patch was negative at first observation and positive later. This, of course, is to be expected in a certain number of cases.

DISCUSSION

In an unselected consecutive group of 207 children ranging in age from 3 months to 3½ years, approximately half of whom were vaccinated with B C G, simultaneous patch and Mantoux tests were performed in an effort to determine the efficacy of the former. So far as we can determine from the literature, this represents the first study of the value of the patch test in children that react to tuberculin following the parenteral administration of B C G. Previous reports[5] concern children known to have or suspected of having active or inactive tuberculosis. It is obvious that, by and large, such persons will exhibit a

greater percentage of highly sensitive individuals than can be found among children vaccinated with B C G. Consequently the reasonable agreement reported here between the Mantoux and patch reactions carries with it the added importance that the patch test gives positive reactions in individuals of a low grade of sensitivity induced by an avirulent tubercle bacillus. It also seems important to stress the fact that the patch test was negative in all cases where the Mantoux was negative. These children came from a milieu with a high incidence of tuberculosis although their immediate family environment was nontuberculous. We believe it distinctly noteworthy that only those children with a positive Mantoux gave a positive patch reaction, and none of the negatives gave a positive patch. This indicates that a falsely positive patch is as rare as a falsely positive Mantoux.

Another point which may be profitably brought up for discussion is the technique of applying the patch. In going back over our results it was noted that a good percentage of the discrepancies occurred early in the series. When the mode of application was more or less standardized so that the several individuals performing the tests were doing them alike, fewer differences appeared. Carefully cleaning the skin with ether or acetone, applying rather severe pressure over the actual patch areas with the thumbs, and warming the entire patch by placing the palm over the area for a minute or two seems to be the method of choice for best results.

As a result of this experiment we have instituted routine patch testing of the children under study. At the present writing some 250 additional tests have been performed, using the patch as a screening test with only one discrepancy; i.e., in one case the patch was negative in a vaccinated child but a subsequent Mantoux with 1:100 dilution of old tuberculin was positive. We have made it routine to repeat a patch that is negative in a vaccinated child with a second patch in an area just below or above the first area, and only if the second patch is negative is a Mantoux performed. It is noteworthy that in eight individuals in whom the first patch was negative, the second was positive in seven. There are two possible explanations for this phenomenon. One is a possible error in technique in the first application or a faulty patch. The other is that offered by Novak[6] for the increased incidence of positive tuberculin reactors upon whom a second Mantoux is immediately performed when the first is read as negative. He cites the possibility of an awakening of a dormant allergic state by the first test which is demonstrated by the positivity of the second test.

SUMMARY AND CONCLUSION

The tuberculin patch test has been applied to 207 children ranging in age from 3 months to 3½ years. These children are being followed as part of a controlled study of the efficacy of B C G vaccination against tuberculosis. Because of the unpleasantness of repeated Mantoux test-

ing in this project, the patch test seemed to offer an opportunity to surmount these objections to intradermal injections. The comparative study reported here indicates a reasonable comparison between the Vollmer patch test and the Mantoux test. These results agree in the main with those reported by others on children of known Mantoux reaction due to a tuberculous process, active or inactive, in whom the degree of reactivity to tuberculin is greater than that following B C G vaccination. This point is discussed in greater detail. Certain factors of technique of application are discussed, as a result of which repatching seems to be indicated before resorting to a Mantoux in order to eliminate possible errors in technique in performance of the first test. Readings on 114 patches at forty-eight and ninety-six hours after application confirmed the impression that accurate readings may be obtained best at ninety-six hours. It seems reasonable to conclude that the patch test may be used as a screening test to indicate positive reactors to tuberculin in children.

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Critical Review

FACTORS INFLUENCING PREMATURE INFANT MORTALITY

With a Review of the Recent Significant Literature

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I. PUBLIC HEALTH CONSIDERATIONS

IN RECENT years, renewed attention has been directed by public health workers toward the problem of the reduction of avoidable infant deaths. Interest has centered mainly in deaths which occur in infants under 1 month of age, and particularly in those who are born prematurely. It is usually estimated that 50 per cent or more of the annual neonatal mortality is directly attributable to prematurity.[1]

The trend in premature infant mortality is broadly presented in Table I which shows the infant death rates in New York City for the decade 1930 to 1939 and reflects the general problem throughout the country.[2] In infants under 1 year of age the mortality rates have declined from 57.2 to 37.1 deaths per 1,000 live births. This decrease is evident mainly in infants from 1 month to 1 year of age; 26.7 to 12.3 deaths per 1,000 live births. By comparison, the mortality rates in infants from birth to 1 month of age show the decrease to be but from 30.6 to 24.8 deaths per 1,000 live births. It is important to bear in mind that about one-half of this neonatal mortality is charged to infants dying from prematurity. This persistent tendency is shown in Fig. 1 which gives the comparative trends from the more important causes of death under 1 month of age. The problem of lowering these deaths in premature infants still constitutes, therefore, a challenge to workers in the field of neonatal mortality.

II. FACTORS IN PREMATURE INFANT MORTALITY

Investigations on the problem of prematurity in general have followed four main avenues of study: (1) Analysis of the predisposing and contributory factors in premature births and deaths; (2) determination of the more direct causes responsible for these births and deaths; (3) verification of the accuracy of the stated causes of death; and (4) formulation of plans to effect a much needed reduction in the incidence of prematurity and in premature infant mortality. These studies have revealed certain important fundamental data. It would seem worth while, therefore, to cull the widely scattered literature and to review those factors which have been found to play significant roles in the continued high death rates among these prematurely born infants.

1. Predisposing and Contributory Causes

A. *Length of Gestation.*—It is generally appreciated that mortality in infants born prior to term decreases as pregnancy approaches nearer to full term. The studies of Clifford[3] have shown that premature infant mortality can be reduced by delaying the induction of premature labor

until a viable baby can be assured. Breese[4] likewise believes that the most important group to consider in reducing mortality in premature infants is that in which deliveries are induced, and that methods must be found to bring these deliveries nearer to term.

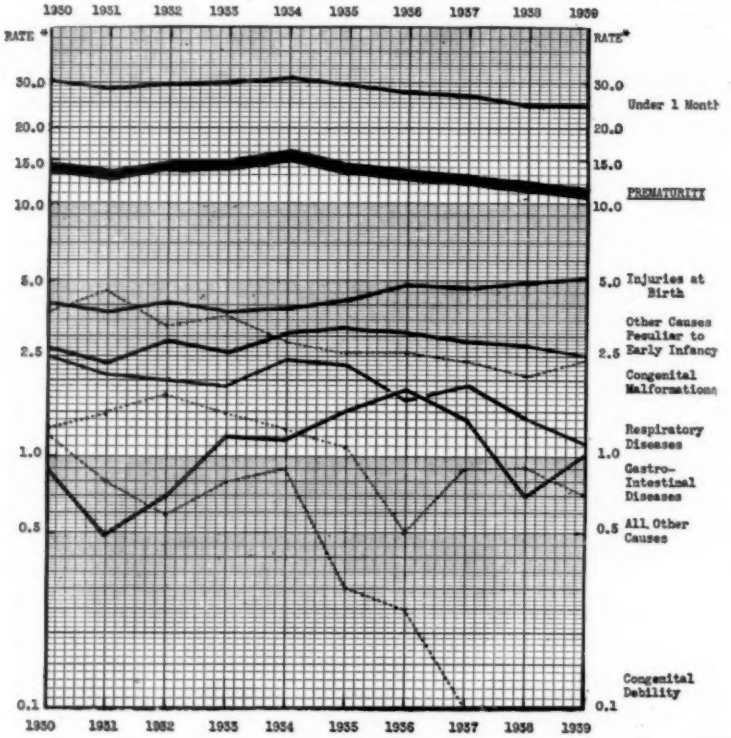

Fig. 1.—Trends in neonatal mortality in New York City from 1930 to 1939. (*Rate per 1,000 live births.)

B. *Birth Weight and Length.*—There is also a decrease in mortality with increase in the weight and the length of the premature infant at birth. Clifford,[3] Breese,[4] and Tyson[5] have shown that mortality in premature infants varies inversely with the weight of the baby; the greater the birth weight, the lower the death rate. Peckham[6] also found decreasing stillborn and neonatal mortality rates with increasing weight and length at birth. The decrease was slow under 1,200 Gm. (2 pounds, 10 ounces) and rapid with weights between 1,800 Gm. (3 pounds, 14 ounces) and 2,400 Gm. (5 pounds, 5 ounces). A relatively stationary level was reached at 2,700 Gm. (5 pounds, 14 ounces). With increasing length at birth the decrease in mortality was steady until a level was attained at 47 cm. (18½ inches). According to Dunham,[7] infants weighing at birth 1,000 Gm. (2 pounds, 3 ounces) or less rarely survive. Where development is anatomically and physiologically adequate, the chance of survival in infants weighing more than 1,500 Gm. (3 pounds, 5 ounces) is, however, four times greater than in infants of a weight of 1,500 Gm. or less at birth.

TABLE 1

INFANT DEATH RATES IN NEW YORK CITY, 1930-1939

YEAR	TOTAL NUMBER OF LIVE BIRTHS	STILLBIRTHS		DEATHS UNDER 1 YEAR		DEATHS 1 MONTH TO 1 YEAR		DEATHS UNDER 1 MONTH		DEATHS UNDER ONE MONTH			
										FULL-TERM INFANTS		PREMATURE INFANTS	
		NUMBER	RATIO*	NUMBER	RATE*	NUMBER	RATE	NUMBER	RATE	NUMBER	RATE	NUMBER	RATE
1930	122,811	5,700	46.4	7,030	57.2	3,277	26.7	3,753	30.6	2,032	16.6	1,721	14.0
1931	115,621	5,579	48.3	6,472	55.9	3,125	27.0	3,347	28.9	1,823	15.8	1,524	13.2
1932	109,878	5,396	49.1	5,594	50.9	2,366	21.5	3,228	29.4	1,692	15.4	1,536	14.0
1933	103,500	5,347	51.7	5,508	53.2	2,409	23.3	3,099	29.9	1,599	15.5	1,500	14.5
1934	101,239	5,070	50.1	5,287	52.2	2,133	21.1	3,154	31.2	1,593	15.7	1,561	15.4
1935	100,657	4,902	48.7	4,790	47.6	1,856	18.4	2,934	29.2	1,537	15.3	1,397	13.9
1936	98,507	4,992	50.7	4,464	45.3	1,733	17.6	2,731	27.7	1,452	14.7	1,279	13.0
1937	101,988	4,847	47.5	4,457	43.7	1,746	17.1	2,711	26.6	1,463	14.3	1,248	12.2
1938	102,045	4,995	48.9	3,909	38.3	1,383	13.5	2,526	24.8	1,326	12.9	1,200	11.8
1939	102,261	6,786	66.4	3,793	37.1	1,260	12.3	2,533	24.8	1,348	13.2	1,185	11.6

*Stillbirth ratio and death rates per 1,000 live births.

TABLE II

PREMATURE INFANT MORTALITY ACCORDING TO POSTNATAL AGE AT DEATH, NEW YORK CITY, 1930-1939

YEAR	TOTAL NUMBER OF LIVE BIRTHS	PREMATURE INFANT DEATHS UNDER ONE MONTH OF AGE							
		UNDER 1 MONTH		UNDER 1 DAY		1 TO 6 DAYS		7 TO 29 DAYS	
		NUMBER	RATE*	NUMBER	RATE*	NUMBER	RATE*	NUMBER	RATE*
1930	122,811	1,721	14.0	963	7.9	491	4.0	267	2.2
1931	115,621	1,524	13.2	852	7.4	382	3.3	290	2.5
1932	109,878	1,536	14.0	930	8.5	393	3.6	213	1.9
1933	103,500	1,500	14.5	831	8.0	439	4.2	230	2.2
1934	101,239	1,561	15.4	821	8.1	471	4.7	269	2.6
1935	100,657	1,397	13.9	837	8.3	379	3.8	181	1.8
1936	98,507	1,279	13.0	758	7.7	350	3.6	171	1.7
1937	101,988	1,248	12.2	772	7.6	341	3.3	135	1.3
1938	102,045	1,200	11.8	792	7.7	303	3.0	105	1.1
1939	102,261	1,185	11.6	800	7.8	302	2.9	83	0.8

*Rate per 1,000 live births.

C. *Postnatal Age at Death.*—A consideration of the factor of postnatal age shows that death occurs during the first twenty-four hours after delivery in about 55 to 60 per cent of the cases (Table II). Between the postnatal ages of 1 to 6 days, inclusive, death occurs in about 30 per cent of the babies, while the remaining infants die at the ages of 7 to 29 days. It will be noted that the death rates in premature infants dying under 1 day of age have remained constant, as contrasted with the marked decline in the age group of 7 to 29 days. The chance of survival in premature infants increases therefore with advance in postnatal age.

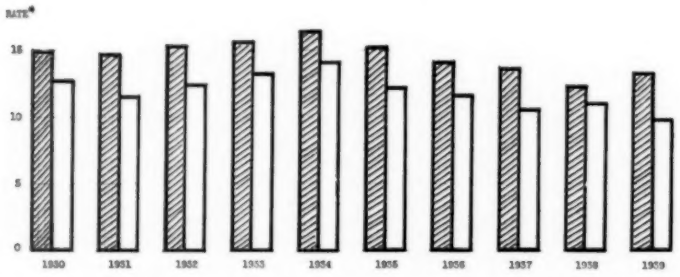

FIG. 2.—Premature infant mortality according to sex, New York City, 1930 to 1939. Cross-hatched bars denote male premature babies; white bars show female premature babies. (*Rate per 1,000 male live births and per 1,000 female live births.)

D. *Sex.*—Fig. 2 shows the differences in premature infant mortality according to sex. The constantly higher rates among the male babies are quite apparent and again demonstrate the universal phenomenon of excess mortality among males as compared with females.[8] While the frequency of premature births is greater in female babies, probably because of their smaller birth weight and birth length, a much higher stillborn ratio and death rate occur in male infants. According to the theory of Lenz,[9] which has been corroborated by others,[10] this excess mortality in males is chiefly the result of the operation of recessive hereditary sex-linked factors.

Further light on this sex difference is shed by the investigations of Ciocco[11] on the sex ratio in stillbirths. Masculinity decreases as the length of uterogestation increases up to and including the seventh month when the masculinity rate is at a minimum; thereafter it increases. As compared to male stillbirths for the same period, a smaller percentage of female stillbirths occurs before the sixth month and after the eighth month of gestation. Ciocco also states that female stillbirths predominate when fetal mortality is essentially the result of defective embryonic development. Male stillbirths are higher when the placental structure is either faulty or inadequate to safeguard the fetus from toxic elements transmitted by the mother. Masculinity is also highest when stillbirths result from a combination of factors among which the relative size of the fetus is of importance.

E. *Color.*—As is indicated in Fig. 3, the mortality in colored premature infants is considerably greater than that in white premature infants. This frequently noted observation serves to emphasize again one of the factors deserving considerable attention in efforts to reduce premature infant mortality.[12] In this connection it should be borne in mind that the incidence of small infants is almost twice as great in the black as in the white race.[6] In addition, the studies of Duffield, Parker, and Baumgartner[13] show that since in the same birth-weight groups no consistent difference can be demonstrated between the mortality rates of white and of colored infants, the higher crude mortality rates of colored babies in comparison with white babies may be attributable to the lower weights of the colored babies.

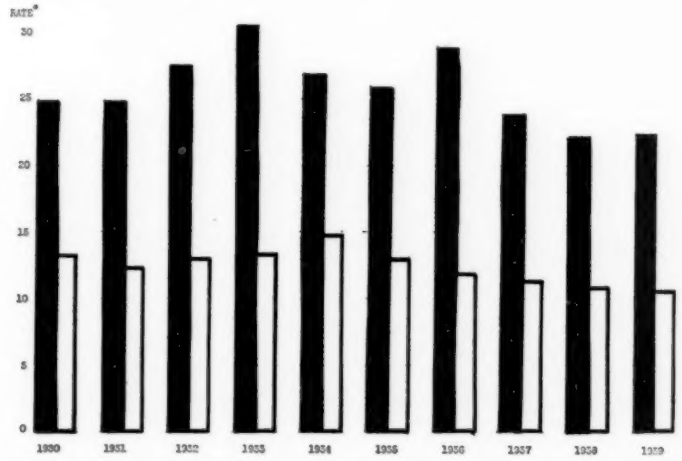

Fig. 3.—Premature infant mortality according to color, New York City, 1930 to 1939. Blackened bars denote colored premature babies and white bars, white premature babies. (*Rate per 1,000 colored live births and per 1,000 white live births.)

F. *Season.*—The seasonal variations in infant mortality are shown in Fig. 4. The marked rise in deaths during the winter and fall months, the period of respiratory disorders, is noted readily in infants from 1 month to 1 year of age. No such outstanding seasonal fluctuation is manifested in the neonatal death rates or in the death rates of infants born prematurely. This trend suggests a certain homogeneity of factors

contributing toward the death of these premature babies independent of seasonal tides in disease, factors probably related more closely to the circumstances surrounding the delivery and birth of the babies. In this connection attention is again called to Table II in which it will be noted that 55 to 60 per cent of prematurely born infants die during the first twenty-four hours of life and about 30 per cent during the postnatal ages 1 to 6 days.

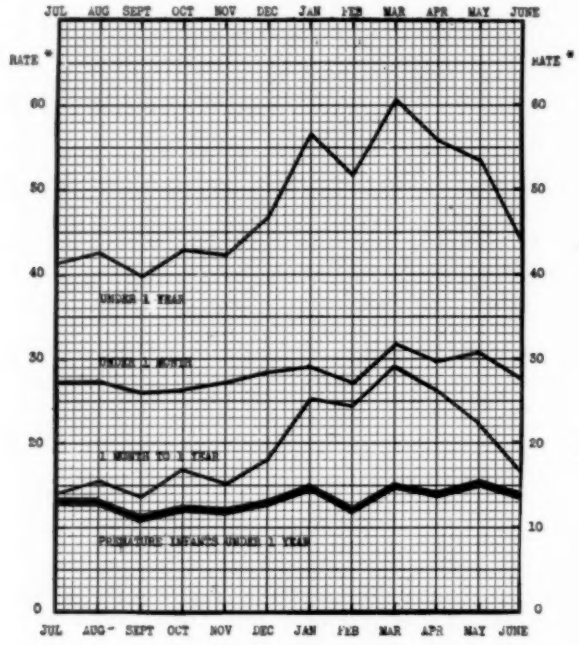

Fig. 4.—Seasonal variation in infant mortality in New York City from 1930 to 1939. (*Average monthly infant mortality rates per 1,000 live births, computed on an annual basis, 1929 to 1939.)

G. *Locality.*—The studies of Yerushalmy[14] have shown that while premature births are more frequent in urban than in rural communities, mortality is higher in the latter areas. It would seem that the benefits derived from the present care of the prematurely born infant can well be extended to meet adequately the requirements of the rural sections of the country.

H. *Familial History.*—According to Gardiner and Yerushalmy,[15] a familial trend is evident in the tendency for babies to be born prematurely, or to be born dead, or to be born so weak that they do not survive the first month of extrauterine life. The neonatal mortality rates and stillbirth rates among infants born to mothers with previous single or multiple infant loss are more than twice those among infants born to mothers with no such previous loss. This increase in mortality varies directly with the number of past infant losses. It is present in every order of birth, particularly in second births, and for every age of the mother. The frequency of premature birth, in itself of repetitive character, follows a similar trend. Mothers with previous premature births, miscar-

riages, or abortions are much more likely to have premature births in succeeding pregnancies than those who had only full-term infants in the past.

An analysis of the birth records of the Buffalo City Hospital shows that of 2,116 mothers who were delivered of full-term infants, there were previously 18 premature births and 86 abortions per 1,000 pregnancies. By contrast, of 221 mothers who gave birth prematurely, there were 50 premature births and 144 abortions per 1,000 previous pregnancies. The investigators state that mothers who have experienced infant loss should be selected for special attention during subsequent pregnancies to conserve wherever possible the life of the offspring. Information should be sought regarding the circumstances which result in the familial tendency to fetal or infant loss. Adair and Potter[16] are also of the opinion that fetal and neonatal disease and death may result from hereditary factors, particularly among premature infants.

I. *Age of the Mother.*—The studies of Breese[4] suggest that the age of the mother has very slight effect on premature infant mortality except in women over 40 years of age. Peckham[6] states that although small babies are born to primiparous women more frequently than to any other group, the mortality rates in these babies are greater with advance in the age of the mother. A similar result was obtained by Tyson[5] who also found little difference in the weights of babies of primiparous as compared to those of multiparous women.

J. *Age of the Father.*—Referring again to the investigations of Yerushalmy,[17] a marked relationship was found between the stillbirth rates and the age of the father. The rates were highest for young and old fathers and low for the intermediary groups, a pattern similar both in male and in female infants. The incidence of premature births by age of the fathers followed the same trend as in stillbirths. It is suggested that the high stillbirth rates associated with young fathers are due almost entirely to the high incidence of premature births, while those associated with old fathers are due both to the high incidence of premature births and to the high stillbirth rates.

K. *Parity of Mother (Order of Birth).*—According to Yerushalmy,[14] the frequency of premature births is high for the first order of births, falls to a minimum for fifth births, and increases thereafter. As to premature infant mortality, it is at a minimum however for first births and rises to a maximum for the order 10 or over. Tyson,[5] Peckham,[6] and Einhorn[18] also obtained a rising mortality rate with increasing parity of the mother as their series approached the group para X.

L. *Puerperal Fatality and Loss of Offspring.*—Recently Yerushalmy, Kramer, and Gardiner[19] studied maternal deaths in relation to the births from which they arise and found a close association between the death of the mother and the loss of the baby. The puerperal fatality rate was 19.3 per 10,000 deliveries when the infant was born alive and 298.7 when the infant was born dead. The stillbirth rate was 27 per 1,000 total births for infants of surviving mothers and 300.4 for infants whose mothers died in childbirth. The mortality both of the infant and of the mother rose sharply in pregnancies which terminated prematurely and was more pronounced for the infants than for the mothers. The puerperal fatality rate was 20.1 per 10,000 deliveries when birth was at term and 141.3 when it was premature. The stillbirth rate for premature infants was 247.8 per 1,000 total births and the neonatal mortality, 373.8. Septicemia was the common cause of

death in mothers who went to term and the toxemias in mothers of the premature infants. The average time between disease and death was 10.9 days for mothers whose infants were born alive and 4.9 days for the mothers of stillborn babies.

M. *Multiple Births.*—The studies of Peckham[6] indicate that stillborn and neonatal death rates are lower in multiple than in single births. In addition, there are no significant differences in the mortality rates of the first as compared to the second sets of twins. Yerushalmy, Kramer, and Gardiner[19] found on the contrary that fatality rates of plural births were three times as high as in single births. Duffield, Parker, and Baumgartner[13] also state that there is a higher mortality rate in multiple pregnancies because of the lower birth weights of such infants.

N. *Socioeconomic Conditions.*—The observations of Einhorn[18] indicate that mortality in premature babies who were born to mothers on ward services compared favorably with that in premature babies who were born to mothers receiving private care. In 1934, the mortality for the former group was 45 per cent and for the latter group, 42 per cent. In 1938, 31 per cent of the general service premature babies and 22 per cent of the private premature babies died.

O. *Hour of Birth.*—The studies of Yerushalmy[20] also show that the stillbirth and neonatal mortality rates are considerably higher for infants born between the hours of noon and midnight than for those born between the hours of midnight and noon. The highest rates occurred between 3 P.M. and 6 P.M. The percentage of deliveries which were operative followed the same trend.

P. *Feeding.*—In accordance with well-known clinical experiences, Wilcox[21] found that there was greater susceptibility to disease and higher mortality rates in premature infants who received little or no breast milk after the first ten days of life.

2. *Direct Causes Responsible for Premature Infant Mortality*

A. *Diseases in the Mother.*—In the causation of premature births and deaths, the maternal complications of pregnancy play important roles. As has been shown by Bundesen and his collaborators,[22] as well as by others, the causes most often leading to premature births are the toxemias and nephritis, heart disease, faulty implantation and premature separation of the placenta, prolapsed cord, external violence, and hydramnios. Multiple births, breech presentations, induced labor, and intrauterine asphyxia may similarly influence adversely the normal termination of pregnancy. Breese[4] is of the opinion, however, that conditions in the mother, such as multiple pregnancy and toxemia, have relatively little effect on mortality in the premature infant who is born alive. The single exception is hydramnios which exerts an unfavorable effect on the premature infant mortality rate. For a more complete survey on the causes of premature birth, reference may be made to the studies of Anderson.[23]

B. *Obstetrical Procedures and Duration of Labor.*—The question of the effect of obstetrical manipulation and the duration of labor on premature infant mortality still remains a problem open to discussion. Tyson[5] noted no relationship between death in prematurely born infants and the length of labor. He also expressed surprise that the lowest mortality occurred in those premature infants who were delivered by forceps and attributed this result to the reduction of the

pressure on the infant's skull by the rigid peroneal muscles. The next lowest death rate was found in premature infants delivered by cesarean section, and the third lowest in those delivered spontaneously. The highest death rate occurred in breech deliveries. Breese[4] also found that the application of forceps afforded the safest means of delivery of the premature infant.

C. *Drugs.*—Of importance in premature infant mortality are the effects of the analgesics, anesthetics, and oxytocics which are used to minimize pain and to promote the rapidity of labor. There is, however, some difference of opinion as to the influence exerted on premature infant mortality by the use of these drugs. Dosage and technique of administration differ widely. It is difficult therefore to draw precise comparisons as to their effects on the infant. Schreiber[24] is of the opinion that the depressive action on the respiratory center of birth analgesics in greater than pharmacologic doses bears a direct relationship to the degree of apnea which is directly related to the severity of cerebral symptoms and damage to nervous tissue. Schreiber concludes that such dosage may be the causative factor in fetal anoxemia with resulting cerebral damage.

As to the use of morphine, Dunham and McAlenney[25] found that of 63 infants who were born to mothers given morphine, 38 per cent died, while of 125 infants whose mothers did not receive morphine, only 23 per cent succumbed. Furthermore, 41 per cent of the babies showed delayed respirations in the group whose mothers received morphine during labor, as contrasted with only 16 per cent in the other group. Breese[4] also cautions against morphine in its effect on the fetus and infant. With regard to anesthetics, the administration of ether is considered the safest. Recently,[26] the indiscriminate use of solutions of posterior pituitary during the early stages of labor was again condemned because of its adverse effects both on the mother and her baby.

D. *Disease in the Baby.*—The chance of survival of the premature will depend in great measure not alone upon its anatomic and physiologic adequacy, but also upon the presence or absence of disease. Certain factors influencing premature infant mortality have already been discussed, such as the degree of prematurity, weight and length of the baby, sex and color. The important roles played by conditions such as birth injuries and congenital malformations and diseases of the respiratory and gastrointestinal systems in determining the survival of the infant have also been reviewed. Attention is called to the investigations of Bundesen and his collaborators[22] which indicate the definite influence on premature infant mortality of the complications of pregnancy, breech presentations, multiple births, asphyxia due to analgesics, and operative procedures. These highly important aspects of the problem will be discussed further subsequently.

E. *Aftercare of the Baby.*—It is also apparent that for the survival of the prematurely born infant every precaution must be taken for adequate postnatal care. Not alone is experienced medical and nursing care essential, but proper equipment must be available for the control of environmental factors. The importance of protecting these highly susceptible infants from infections is well recognized. It is surprising however that only recently has active attention been given this phase of the problem. The investigations of Frant and Abramson[27] have disclosed the prevalence of communicable diseases in the nurseries of lying-in hospitals and the high toll of life, particularly in premature infants, which these infections exact. Measures to combat these avoid-

able infant deaths have now been instituted in such cities as New York[28] and Chicago. In brief, these measures provide for individualization in all phases of care of the infant and for avoidance of concentrations of babies in dormitory nurseries, as well as for the institution of techniques of aseptic nursing.

In addition, the work of Blackfan and Yaglou[29] stresses the importance of maintaining optimal temperature and humidity control at ranges higher than that needed in the care of the normal full-term infant. A nursery temperature of from 75 to 100° F. and a humidity of about 65 per cent seem best suited to stabilize the body temperature of premature infants. Many varieties of incubators have been made for the control of these factors. These contrivances have also been fitted to serve as artificial respirators and for the administration of oxygen and carbon dioxide. In actual practice it would seem that their complicated construction precludes of efficient operation unless operated by a thoroughly trained personnel. In ordinary circumstances simpler apparatus would probably serve to much better advantage.

As has been pointed out by Dunham,[30] the prevalent neonatal mortality rates indicate that comparatively little progress has been made in knowledge of the care of premature infants during the past thirty years. However certain essential data have slowly accrued. The studies of Hess[31] and his associates represent a considerable advance in the feeding and nursing care of the premature infant as well as in the later phases of growth and development. A better knowledge of the physiology of the premature infant has been contributed by Benedict and Talbot[32] on caloric and fluid requirements in relation to body weight and environmental temperature. Gordon and Levine[33] have shown furthermore that the basal metabolic rate of premature infants as expressed in calories per kilogram closely approximates and in calories per square meter is less than that of the full-term infant of a comparable age. When referred to surface area, the lower rate may denote intrinsic abnormality of heat production due to larger surface area exposed in relationship to mass of heat producing tissues. Tidwell and his co-workers[34] have found that in premature infants fat splitting is less complete and that fats such as olive oil and soy bean oil are better absorbed than butterfat. Absorption is also favored by the presence of more than one double bond in the fatty acid chain.

In the studies of the blood of premature infants, Darrow and Cary[35] have shown that the total protein is low because of a lower content of globulin. Josephs[36] has stressed the importance of early therapy in the prevention of anemia in the premature infant. In the field of the vitamins, the necessity for the administration of larger amounts of a vitamin D preparation to premature infants as compared with that required by full-term infants in the prevention of rickets is well known.[37] Likewise, recent work has demonstrated the value of early use of vitamin C[38] in premature infants as well as the selective use of vitamin K[39] in certain hemorrhagic states. And lastly, the investigations of Potter[40] and of Einhorn[41] suggest a possible connection between endocrine deficiency and survival in premature infants. These studies have indicated that the blood of newly born infants contains comparatively large amounts of estrogenic substance which is rapidly excreted by the kidney so that the urine is estrin-free in about four days. The administration of the estrogenic substance is believed to supply this deficiency and to induce a stimulating effect on the infant with respect to weight and general favorable progress.

3. *Verification of the Accuracy of the Stated Causes of Death*

The frequency with which premature birth is given as a primary cause of death merits further consideration. Is it true that about 50 per cent of the neonatal deaths is due directly to prematurity, or is it more likely that certain fundamental physiologic or pathologic conditions underlie these deaths? Prematurity is a most convenient diagnosis to make. Since it is considered a leading cause of death in early infancy in the International List of Causes of Death, the diagnosis of premature birth or prematurity is acceptable to health departments, no further explanation being required. Too often, however, the term premature birth masks the true cause of death.

As has been shown by the studies of Bundesen and his co-workers[22] and Potter,[42] it is more and more apparent that except in cases of very marked prematurity physiologically incompatible with life, infants born prior to term do not die from prematurity alone, but rather from some underlying pathologic process. The term premature birth merely refers to the degree of anatomic and physiologic maturity with respect to the temporal factor. These infants die from conditions and infections to which the stress of prematurity predisposes them. The investigators have also revealed glaring discrepancies to exist when the diagnoses as given on death certificates are compared with those found by careful analysis of the case history records and by post-mortem examinations. While the latter do not in every case reveal the underlying causes of death, the existence of disease is found with sufficient frequency to warrant the discarding of the diagnosis of prematurity as a primary cause of death.

4. *Campaigns to Reduce Premature Infant Mortality*

In recognition of the importance of the problem of premature infant mortality, certain large cities, notably Chicago, have made excellent progress in the improved care of the premature infant. As elaborated by Hess,[43] these plans call for the immediate reporting by telephone to the health department of all premature births. This preliminary report is followed by written confirmation within twenty-four hours. Certain large institutions, such as the Sarah Morris Hospital, have been equipped and were designated to offer the following services:

1. Ambulance service by the hospital, specially heated bags being provided.
2. Premature ward care with special equipment for oxygen therapy and other types of emergency therapy.
3. Nursing service by a trained personnel.
4. Breast milk from wet nurses and visiting mothers.
5. Field nursing service for instructions of mothers, special attention being given to the promotion of breast milk secretion.
6. A supply of a simple type of heated bed for use by graduates in the home.
7. An outpatient clinic for instruction of mothers and the care and supervision of graduates not having private physicians.

It is most surprising that this city-wide plan in Chicago has not received greater application throughout the country, particularly in view of the magnitude of the problem. Not all institutions are equipped nor their personnel sufficiently trained to cope with the premature

infant. Merely having equipment does not necessarily indicate ability to care for the premature infant. A trained personnel is essential.

Furthermore, there should be a unified plan adopted throughout the country so that results may be adequately compared. This plan should provide for prenatal, intrapartum, and postpartum care of the mother and complete care of the premature baby. Special premature infant clinics and premature infant nursing services should be established similar to those elaborated in Chicago. The plan should not be formulated merely to suit local conditions but should be broad enough to provide for country-wide application.

III. COMMENT

In general, the studies reviewed indicate the outstanding factors deserving special emphasis in plans to ensure the survival of prematurely born infants. The investigations, however, have proceeded along independent lines and mainly have considered the problem in connection with local conditions. A surprising lag has occurred in piecing the results into a broad and uniform nation-wide plan to reduce premature births and deaths. This lag may be attributed to several factors.

1. *Criteria of Prematurity.*—The exact criteria which constitute prematurity are still open to discussion. Many measures of judgment are employed either singly or in combination. According to Dunham,[7] in the estimation of fetal maturity, a fetus of less than 28 weeks gestation is usually regarded as nonviable. The span of the prematurely born infant is placed between the twenty-eighth and the thirty-eighth week of gestation, while beyond this time to the fortieth week the fetus is considered mature. The line dividing the nonviable fetus and the premature viable infant has been defined as follows:[44] "The term *premature labor* should apply to the delivery of a fetus capable of surviving, and as usually understood, but not absolutely limited in fact, to apply to the product of conception after 28 weeks or 6½ calendar months or seven lunar months, which in American experience will usually have a weight of 1,500 Gm., or 3¼ pounds, and a length of 35 cm., or 14 inches."

Added criteria in the recognition of prematurity are: (1) A birth weight of 2,500 Gm. (5 pounds, 8 ounces) or less; (2) a crown-heel length of 47 cm. (18.5 inches) or less; (3) a relatively greater disproportion between the head and chest circumference or head and shoulder girth than is found in the full-term infant; (4) an occipitofrontal diameter of the skull of less than 10 cm. (3.9 inches); (5) a foot length of 7 cm. (2.8 inches) or less; and (6) roentgenographic evidence of absence of certain centers of ossification in the long bones. As a single standard, the birth weight has gained priority, a newborn infant of a body weight of 5 pounds, 8 ounces (2,500 Gm.) or less at birth being considered premature. Potter and Adair[42] have advanced the following criteria to determine the maturity of the fetus or infant. These standards are based on Scammon's estimates for weight and length in relation to the menstrual age of the fetus, the fetus being placed in the group in which at least two of the three criteria apply.

I. Abortion:

1. Less than 400 Gm. in weight
2. Less than 28 cm. in length
3. Less than 22 weeks (missed abortions excluded)

II. Premature:

A. Previable:
1. From 400 to 999 Gm. in weight
2. From 28 cm. to 35 cm. in length
3. From 22 to 28 weeks

B. Viable:
1. From 1,000 to 2,499 Gm. in weight
2. From 35.1 to 47 cm. in length
3. From 29 to the end of 37 weeks

III. Term:
1. From 2,500 to 4,499 Gm. in weight
2. From 47.1 to 54 cm. in length
3. From 38 to 42 weeks

IV. Postmature:
1. More than 4,500 Gm. in weight
2. More than 54 cm. in length
3. More than 42 weeks

While any of these criteria may have immediate practical value, it is necessary that complete agreement be arrived at in the more uniform appraisal of the degree of maturity of the newborn infant or fetus. The standards should be those most readily obtained by the clinician in order to facilitate comparison of the many studies on the causative factors in premature mortality.

2. *Prematurity As a Reportable Condition.*—Furthermore, much indefiniteness prevails with regard to the true extent of premature births, the frequency being variously estimated from 3 to 10 per cent. It is usually only where special studies are carried out that this information is available. Few organized health districts make prematurity or premature birth a reportable condition. Statistical analysis of premature infant death rates based on actual live premature births therefore cannot be made. It would seem that in order to plan effective campaigns to reduce mortality in infants born prior to term, it is of importance at the outset to gain a basic knowledge as to the true extent of such births throughout the various sections of the country. Not only should frequencies be compiled, but all pertinent data, such as sex, color, race, season, order of birth, and the circumstances underlying each premature birth, so that proper weight and emphasis can be allocated to each factor in plans to reduce death in these babies.

3. *Prematurity As a Cause of Death.*—This aspect of the problem has been considered in detail previously. It is, however, of sufficient importance to call attention again to the fact that the term prematurity is not a diagnosis but registers only a statement of time. Until more complete and accurate clinical and pathologic studies are routinely made in each instance, the true causes underlying death in these infants will always remain in doubt. It would perhaps be good public health practice to make every death in a premature baby the subject of a medical examiner's investigation to inquire carefully into the circumstances causing this mortality. Potter[42] states that at necropsy of premature infants most lesions sufficient to cause death fall into five major groups: (1) Hemorrhage, either visceral or intracranial, usually caused by trauma; (2) anoxemia; (3) malformations; (4) in-

fections; and (5) idiopathic conditions. Atelectasis is not regarded as a cause of death. At times it may be difficult to determine pathologically the cause of death in premature infants. In Potter's series of some 2,000 necropsies, about 25 per cent revealed no evident pathology. However, even in these cases a diagnosis of the cause of death may be possible if the fact is not lost sight of that not alone may there be an anatomic inadequacy, but also a physiologic inadequacy incompatible with life.

4. *Stillbirths.*—The situation is also complicated by the premature births which are listed under the category of stillbirths. At present no attempt is made to divide the infants in this designation into full-term stillbirths and premature stillbirths. Much information of value is thereby lost for consideration by public health workers. Dunham and her collaborators[45] emphasize that there is no acceptable classification of the causes of stillbirths which include rules for assignment of cause. There is furthermore no single definition of stillbirth in general use, and the period of gestation required varies greatly. Premature stillbirths merit the same minute clinical and pathologic study that should be given to deaths occurring among premature liveborn babies.

5. *Listing Premature Infant Deaths.*—Rather than further obscuring the causes of death in prematurely born infants by the indiscriminate use of the vague term prematurity, a better listing should be adopted to clarify the situation.[46] Rates should be calculated both for premature infant deaths and premature stillbirths on the basis of actual premature live births. As a suggestion for statistical purposes, the deaths could then be placed roughly in the following main categories:

I. Premature infant death
  A. Cause determined
    1. In infant
      a. Clinical diagnosis
      b. Pathologic diagnosis
      c. Physiologic diagnosis
    2. Maternal complication of pregnancy (specify)
  B. Cause undetermined

II. Premature stillbirth
  A. Cause determined
    1. In infant
      a. Clinical diagnosis
      b. Pathologic diagnosis
    2. Maternal complication of pregnancy (specify)
  B. Cause undetermined

The main objective to strive for is a determination of the cause of death on a clinical, pathologic, or perhaps physiologic basis. Careful study in the majority of instances will reveal the true underlying causes of death in these infants.

Furthermore, statistical data concerning premature infant mortality should be separated from the usual category of neonatal mortality and a distinct classification erected, listing the various verified causes of death in the premature baby. Similarly, premature stillbirths should be considered separately so that this material is not lost for future study. A better visualization and concept of the trends in the causes

of premature infant deaths and in premature stillbirths would thus be provided. It is also evident that a more rigid application and accurate interpretation are needed of the International List of Causes of Death and of the Manual of the Joint Causes of Death in listing deaths from premature births and in assigning proper precedence to multiple causes of death in these infants.[46] Although it is commonly stated that 50 per cent or more of the neonatal deaths are due to prematurity, a reconsideration of the causes actually responsible for death in these infants would materially reduce this percentage to the correct level.

IV. SUMMARY AND CONCLUSIONS

One of the outstanding problems in the preventive medicine of today is that of the reduction of avoidable deaths in prematurely and immaturely born infants. Despite modern advances in public health comparatively little progress has been made in lowering the death rates in these babies. About one-half of the annual neonatal deaths still occur persistently in infants born prior to expectant term, and from 50 to 60 per cent of these babies die within the first twenty-four hours after delivery. This record is far from encouraging and stands as a distinct challenge to obstetricians, pediatricians, and public health workers.

In recent years an extensive literature has accumulated pertaining to the many complex phases of the problem of premature infant mortality. The more important of these investigations are reviewed in an attempt to integrate the available pertinent data. Stress is laid on those factors which may play significant roles in predisposing or contributing to mortality in premature infants. In addition, due attention is given to investigations directed toward determination of the true causes responsible for death in these babies.

A consideration of these studies serves to emphasize the complicated nature of the problem of prematurity. Furthermore it is apparent that present plans to lower mortality rates from prematurity are based insecurely on rather incomplete knowledge. It is also evident that much fundamental work remains to be done to clarify a perplexing situation. Possible reasons for this confusion are discussed and suggestions made which perhaps may be of value in the solution of the problem of lowering mortality rates in the premature infant.

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American Academy of Pediatrics

Proceedings

TENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

MEMPHIS, TENN.—Nov. 18-20, 1940

Round Table Discussion on Diarrhea and Dysentery

Chairman: Warren W. Quillian, M.D., Coral Gables, Fla.

Associates: W. Eugene Keiter, M.D., Kingston, N. C.
Matthew Winters, M.D., Indianapolis, Ind.

Secretary: H. Chandler Clark, M.D., New Rochelle, N. Y.

CHAIRMAN QUILLIAN.—Dysentery or bowel trouble is a term first used by Hippocrates to describe the passage of frequent stools containing pus, mucus, and blood, and accompanied by straining, or tenesmus. This condition may be associated with disease outside or within the intestine. Obviously if the cause of the condition is found to be outside of the intestine, management becomes a problem of eliminating the original cause, if possible, and at the same time directing symptomatic treatment for relief of the diarrhea, which is secondary. Careful study of each individual case is required, because it is important to determine the inciting cause. Diarrheal diseases represent the most frequent form of disturbances in infancy; and the infant mortality from these is greater than all the acute infectious diseases combined.

Many diarrheal disorders can be prevented. Lyon, who conducted a discussion similar to this one at the meeting of the Academy in Cincinnati in November, 1939,* has offered a classification based upon related initiating factors.

There is a definite relationship between community sanitation, cycles of rainfall, and the prevalence of the common housefly and the incidence of outbreaks of infectious dysentery.

Infants are more likely to develop diarrhea than are adults. This is due primarily to a difference in digestive juices, especially those of the stomach and upper digestive tract. The artificially fed infant subsists almost entirely upon milk with added starch or sugar during the first few months of life. Both milk and sugar solutions are excellent media for the growth of bacteria. Milk, unless produced under clean conditions and sterilized before use, contains many bacteria, some of which may be harmful to the infant. There are factors other than food and bacterial conditions in the intestinal tract which may lead to diarrhea. Some infants have hypermotile intestines, rendering these muscles more sensitive in their response to irritants, to nervous factors, or to parenteral infections.

Diarrhea which occurs in well-nourished, breast-fed babies as the result of temporary overfeeding or associated with an infection elsewhere in the body is usually not accompanied by severe constitutional symptoms. The usual story is that, during hot weather, after improper feeding or following fever, the number of stools

*J. Pediat. 17: 680, 1940.

gradually has increased. This gradual onset is quite different from the picture observed in so-called colitis or dysentery (bacillary) which is a true infection and potentially more dangerous. The stools in the first case are watery and large; they contain no blood or pus, but they do contain large amounts of mucus. In the latter case, the onset is sudden. The mother can remember that when she gave the baby his bottle at one feeding, nothing was wrong. At the next feeding, he refused to eat and apparently had fever. When she forced the milk, he vomited. Within a few hours she noticed that instead of his usual one stool there were three or four during the afternoon. The next day there may be fifteen or thirty stools, small but containing blood and pus as well as mucus; and their passage may be accompanied by tenesmus. Of greatest value is the nature, type, and severity of the diarrhea in a given case.

Now, let us consider in more detail the various specific clinical entities associated with diarrhea and dysentery.

DR. KEITER.*—Diarrhea and enteritis rank next to prematurity as a cause of infant deaths in North Carolina and this has been true consistently for many years. In 1938 the mortality in North Carolina was higher than in any of the preceding four years. The figures for 1939 are not yet available. The infant mortality rate in North Carolina from this cause is approximately double that for the nation as a whole.

There are very obvious reasons for this to one familiar with the economic and domestic conditions among a large portion of the tenant farmer population. Absence of screens, lack of refrigeration, primitive means of heating water and cooling food, and pollution of soil by human excreta are the main factors. In the cities of North Carolina the disease is much less frequent and among people in the higher economic brackets it is all but unknown. The babies of the tenant farmer population are chiefly the ones who succumb to this infection. This situation is not peculiar to North Carolina but is familiar also to those in other portions of the South where such economic and domestic situations prevail.

It is apparent to those of us dealing with these infants that these deaths are due to real dysentery infections. For example, Dr. A. Graeme Mitchell and nine associates report bacteriologic diagnoses on 209 patients requiring 11,530 plates of media. Positive identification of a pathogenic organism was made in only 49 per cent of the patients. The objection can be raised, justifiably, that we are not dealing with proved cases of bacillary dysentery. If, however, one prefers to regard our cases as possibly being interspersed with nonspecific forms of diarrhea, then the results are even more striking because, if anything, the nonspecific forms of diarrhea are even more difficult to control and may have a higher mortality than true bacillary dysentery. Also, a bacteriologic diagnosis cannot be carried to completion in less than three to five days. Our patients, as a rule, are definitely recovering in this time and we would not in any instance wait for such a diagnosis before starting treatment. Then, too, it has not been established yet that treatment should be varied, depending upon whether the infecting organism is Flexner, Shiga, Sonne, or some other variety of bacillary dysentery.

The annual epidemic of dysentery infections usually strikes North Carolina in May and June. Cases continue to occur through July, August, September, and even into October in smaller numbers. In 1936 there were 26 infants admitted to our hospital because of dysentery. We had 10 deaths and performed 4 autopsies in this group. Four of the deaths occurred within a few hours after admission. In 1937, of 17 patients admitted, we had 3 deaths and performed 3 autopsies. In 1938, of 23 admissions, we had no deaths in patients who had been under our care as long as twelve hours. There were 4 deaths, 1 due to bronchopneumonia complicating the dysentery proved by autopsy, the other 3 occurring from a few minutes to seven hours after admission. In 1939 only 6 patients were admitted and 2 deaths oc-

*See North Carolina M. J. 2: 479, 1941.

curred. One died two hours after admission. The other was autopsied and showed the pathologic findings of a fairly mild dysentery complicated by bronchopneumonia, pertussis, and mastoiditis. Many infants were treated as outpatients in 1939 who formerly would have been admitted to the hospital. They were just as sick as any ever treated in the hospital but because of improved methods of management and confidence in these methods, we allowed the patients to come in daily for treatment and observation. Time and again subcutaneous fluids and transfusions were given and the patients allowed to return home promptly afterward. No harmful effects were ever seen following this procedure. In approximately 90 patients treated, 47 transfusions were given in this manner. There were no deaths among the outpatients.

Pathology.—Most notable of autopsy findings is the necrosis of mucosa lining the terminal ileum and the large bowel. All of it is very swollen, thickened, and red, showing areas of hemorrhage and ulceration and large plaques of exudate. The Peyer's patches of the ileum show swelling and ulceration, and also the lymphoid nodules of the large intestine. The ulceration is not limited to these lymphoid structures but occurs also in other areas of the mucosa. The mesenteric lymph glands show tremendous swelling and dusky redness.

It is amazing with what rapidity these changes can occur. For example, one infant was autopsied with a history of only twenty-four hours' duration of symptoms, yet we found the mucosa of the large bowel almost completely destroyed. The greatly swollen, hyperemic bowel readily may explain the cessation of stools and signs of ileus which occur often in fatal cases. One could not expect such a bowel to exert effective motor activity.

Symptoms and Signs.—The onset is usually sudden. Frequently there is extremely high fever and vomiting. Some six or twelve hours may elapse before diarrhea begins. Diagnoses may be rather confusing in these early stages. Not infrequently tetany may appear with chills, and cyanosis or the extremely high fever and toxemia may usher in convulsions which can be rapidly fatal unless promptly relieved. The diarrhea is characterized by numerous small green stools, often tinged with blood and mucus. There may be as few as ten or as many as fifty in twenty-four hours. Fifteen to twenty are average. Dehydration usually occurs because of the vomiting, refusal of water, and the fluid loss in the stools. This also can occur with surprising rapidity. If unrelieved, acidosis may soon follow. Apparently dehydration and acidosis can reach such an extreme degree that irreversible changes occur. Such infants seem doomed to die despite the prompt intravenous restoration of fluids and electrolytes. Such deaths occur within twelve hours after treatment is started and invariably are cases poorly managed at the onset.

While diarrhea is the most characteristic symptom of the disease, the frequency of the stools is not a true measure of its severity. Abdominal distention, often with a reduction in the number of stools, indicates an unfavorable course. Sometimes this results from administration of paregoric which aggravates the distention. Not infrequently abdominal distention is so great that the abdomen feels "doughy" like that in generalized peritonitis. The stools may cease altogether terminally; this is easily understood when one examines the bowel at the autopsy table.

When the disease enters the chronic stage, which may last for weeks, infants become steadily more emaciated and there is failure to gain. The abdomen becomes very large and while there may be not more than three or four stools daily, they are very foul and are large in volume. Poor appetite and poor assimilation of food may lead to nutritional edema. Anemia of some degree is universal among such infants, and they succumb frequently to respiratory complications.

CHAIRMAN QUILLIAN.—Geographic distribution of various types of bacillary dysentery is interesting. Lyon reports that during the period 1920 to 1930, the Flexner strain was found in 80 per cent of the positive cultures and the Sonne type in almost all of the remaining 20 per cent among cases studied in West Virginia.

The Shiga strain was very rarely found either in this group or in Baltimore during the period 1918 to 1923. At Memphis, the Shigella organism is frequently recovered upon culture, as reported by D. E. C. Mitchell.

DR. WINTERS.—The situation in Indianapolis is similar to that of North Carolina indigent. Patients are extremely sick, neglected and dehydrated. Because of these conditions there is a high mortality. During the years 1936, 1937 and 1938 there were fifty-two cases of Bacillary dysentery, forty-four cases of Flexner and two of Shiga.

CHAIRMAN QUILLIAN.—Shiga, in 1898, isolated the bacillary dysentery organism and discovered the glutinations in the blood serum of patients from whose stools it was obtained. All except Shiga ferment mannite. Shiga is not agglutinated by sera of other three types (monovalent).

Toxins of dysentery bacilli are soluble exotoxin, neurotropic, heat labile, and endotoxin, produced by cell autolysis in the intestine, heat stabile.

Pathologically, the exotoxin produces lesions in the central nervous system similar to those of poliomyelitis or encephalitis (gray matter and anterior horns). The medulla and cervical cord are affected principally: hyperemia and hemorrhages, perivascular infiltration with round cells, and cerebral edema in fulminant infections.

The endotoxin produces changes in the gastrointestinal tract (large intestine). Because of slower peristalsis and greater stasis, there are greater growth of organisms, autolysis, and disintegration with liberation of endotoxin. Mucosa, hyperemic and swollen; blood vessels, dilated; necrosis with hemorrhages and fibrin; ulcer healed by scar tissue with narrowing of lumen.

As to the other organs, the liver shows toxic degeneration, the adrenal is congested and necrotic, and joints, if involved, may be of allergic pathogenesis.

Stool cultures, if positive, are diagnostic. Cultures should be done at once, early in the disease on freshly passed specimens. Many cultures may be necessary. Often the culture becomes negative in the second or third week of the disease.

The entire specimen and napkin may be sent to a laboratory at once. Five or six loops of blood and mucus emulsified in 3 or 5 c.c. of sterile broth or normal saline should be obtained; then this emulsion should be streaked on differential agar plate (eosin, methylene blue, lactose agar) and put in the incubator for from eighteen to twenty-four hours.

Differential Diagnosis.—Distinction between dysentery and diarrhea: nature, type, and severity.

Blood: If passed separately or before stool, probably anal local condition; if intimately mixed, rectum or above; if fresh blood, distal segments of intestine.

Mucus: Normal secretion of colon.

Pus: Very significant.

Pain: Right half of colon, griping, colicky; distal segments of colon, tenemus, straining.

Emaciation, loss of sight, anemia.

General physical examination (order important):

1. Digital examination of rectum.
2. Examination of stools and rectal discharges:
   - A. Ulcerative colitis, much pus.
   - B. *B. dysentery*, little pus, much mucus.
   - C. Typhoid, may be bleeding.
   - D. Amoebic dysentery: brick red, liquid stools.
   - E. Intestinal tuberculosis not pathognomonic.
   - F. Food poisoning, staphylococci.
   - G. Polyposis or cancer, blood.

3. Proctoscopic: Ulcerative colitis, tuberculosis, amebiasis, diverticulitis, functional disorders.

4. Roentgenographic: Purgative, irrigation, and empty bowel, then barium enema, evacuation and insufflation with air. Do this before gastrointestinal series.—Bargen—Mayo Clinic.

5. Other procedures:

A. Gastric analysis.
B. Investigate allergy.
C. Blood culture (typhoid).
D. Widal test (typhoid).
E. Blood smears.

Clinical Symptoms—

A. Acute febrile illness associated with frequent passage of loose stools containing mucus, blood, or pus. Different types vary in severity: Shiga worse; Sonne least severe. Also intensity varies with same organism in different geographic locations and according to physical condition of patient.

B. Incubation, one to eight days—shorter in rapidly growing strains.

C. Onset: fever, anorexia, abdominal pain (?).

D. Diarrhea after twelve to thirty-six hours. Ten to twenty-five stools per day with blood and pus (polymorphonuclear cells on smear).

E. Fever 102 to 104° F., three to four days, then lysis.

F. Vomiting early after.

G. Oliguria or anuria unless adequate therapy. Albumin casts (granular) or pyuria.

H. Blood: Leucopenia or normal. Secondary anemia.

I. Central Nervous System: Convulsions, meningismus, headache, probably due to cerebral edema.

Physical Examination: Loss of weight, dehydration, acidosis, scaphoid abdomen, prolapse of rectum.

DR. A. G. JACOBS, MEMPHIS.—Of the 148 cases of dysentery examined, 93 were of the bacillary type, 41 of the parenteral type, and 14 of the typhosus type. We found that Flexner type was largely predominant.

In May there were 5 cases; in June, 56 cases; in July, 30 cases; and in September, 2 cases. With reference to age groups, 13 cases were from 1 to 6 months of age; 28 cases, from 6 to 12 months; 34 cases from 1 to 2 years; 9 cases, from 2 to 3 years; and 9 cases, from 3 to 9 years. As to race, there were 69 colored and 24 white. As to sex, there were 54 males and 39 females.

Dr. Winters, do you see a case of amoebic dysentery often among children in Indianapolis?

DR. WINTERS.—There are no amoebic cases in Indianapolis.

DR. J. L. BORLAND, JACKSONVILLE, FLA.—There is a high incidence of dysentery among pilots of airlines. This is due probably to the increase of air traveling from South America.

CHAIRMAN QUILLIAN.—An interesting clinical differentiation between bacillary and amoebic dysentery in addition to the laboratory phase of the diagnosis is to be found in the mode of onset, history, and appearance of the ulcers upon proctoscopic examination.

In amoebic dysentery emetine is very effective in acute cases: alkaline in intestinal tract facilitates action. Inject parenterally, intramuscularly; usual dosage for adult, ½ gr. twice daily five to ten days. Do not repeat for at least four weeks. Deek's treatment with huge doses of bismuth subnitrate, teaspoonful every three hours.

In amoebic dysentery it is safe to say that if diarrhea is not controlled by emetine, look for another cause. The degree of ulceration depends upon virulence of organism and resistance of host. *Entamoeba histolytica* is only amoeba that will produce dysentery or hepatic abscesses.

Cysts are resistant. They may live for months in water or pass through the gastrointestinal tract of the fly without injury. Motile or vegetative forms die easily. The fly can spread the disease, water can spread the disease. Food contaminated by carriers is most common form of spread.

Incubations, five to ninety-five days. Diagnosis made by finding parasites in stool, especially after epsom salts. Repeated stool examinations four months after cessation of treatment.

Treatment of Amoebic Dysentery—Acute Stage:

1. Emetine hydrochloride, 1 gr. twice daily for three days; repeat after interval of one week.
2. Treparsol, 1 tablet (0.25 Gm.) with meals for four days; repeat every ten days.
3. During intervals of ten days 1 capsule vioform (0.25 Gm.) t.i.d.p.c.
4. Bismuth subcarb., teaspoonful t.i.d.p.c. if abdominal distress and pain is severe.
5. Diet: low residue—fluids, etc.

Carriers best treated with three doses of treparsol or vioform.

There is a parallel decline in so-called simple diarrheas in those communities in which measures are adopted to control the spread of an epidemic of dysentery. This fact leads one to believe that there may be organisms or bacterial agents unknown to us which are responsible for so-called noninfectious or simple diarrheas. Therefore our classifications must necessarily be flexible and approximate in value.

Dr. George N. MacDonnell, City Health Officer at Miami, has obtained some interesting statistics concerning the incidence of bacillary dysentery in South Florida. You will note that much of the "summer" diarrhea occurs during the winter when there is an annual influx into this resort area of many thousands of visitors.

Dr. George M. Lyon has emphasized the importance of the common housefly as a potent factor in the spread of typhoid and bacillary dysentery. Community sanitation, diaper control, isolation, and screening are of tremendous value in prevention. We will discuss management of the actual case later. Conservative efficient handling of the individual early is the keynote to success in treatment.

Much has been written during the past two years concerning various epidemics of diarrhea among the newborn in hospital nurseries. Fortunately, during the past fifteen years we have experienced no epidemic of this character in the hospitals of Miami. We were unable to obtain any information from the records of the Jackson Memorial Hospital (City) or the County Hospital.

Dr. Lyon reported an epidemic of diarrhea among the newborn concurrently with a community epidemic of acute influenza. The fatal cases presented at autopsy were evidence of intracranial lesions, including petechial hemorrhages and cerebral edema. Observers felt that there was a definite relationship between the diarrhea and the influenza epidemic but could demonstrate no actual bacterial invasion.

Many types of diarrheal disorder can occur during the newborn period. Bacillary dysentery has been observed. This age period, however, constitutes a phase of development about which many specific factors are not fully understood. Immunologic response to infection, the effect of viruses, and the individual response to these constitute some of these factors.

Other diarrheas of known etiology due to improper food and faulty sanitation are recognized and fairly well controlled. Better understanding of nutrition, storage of food, refrigeration, production and handling of milk, etc., previously reduced incidence of diarrhea. Recent outbreaks of this epidemic diarrhea have influenced trends of infant mortality. Varied group of organisms have been isolated.

Possibility of skin as portal of entry for the infection or may be due to organism of virus not yet demonstrable.

General findings are those associated with any other wasting disease of early infancy, such as otitis media, bronchopneumonia, congestion of dura, but nothing characteristic. There is no tendency of the disease to spread to older children or adults nursing the affected infants. Most cases are north of the temperate zone; no marked seasonal incidence of reported cases.

Treatment.—Early recognition and prompt energetic effort to combat fluid loss, acidosis, etc. Restriction of food, twelve to twenty-four hours. Subcutaneous Ringer's, Hartmann's or N/saline by continuous drip preferable. When fluid content and protein level is restored, whole blood or serum transfusion. No serum, vaccine, or drugs except possibly sulfanilamide.

Control—

1. All diarrhea of newborn should be reported to Department of Health.
2. Individual care of babies in nursery with surgical asepsis, involving principle of dilution.
3. Cleanliness and sterility of food and equipment used by the baby.
4. Attendants masked, capped, and scrubbed.
5. Aseptic nursing care should include mothers and maternity ward personnel.
6. Surgical asepsis and individual management.

Dr. Winters, do you observe more or less diarrheal disorders now than ten years ago?

DR. WINTERS.—Less.

CHAIRMAN QUILLIAN.—To what do you attribute this decreased incidence?

DR. WINTERS.—Our ability to make an early diagnosis, improved methods of food preservation and refrigeration, handling of milk and water control, public health and education, including screening agninst fly and other pests.

CHAIRMAN QUILLIAN.—Proper preparation of the infant's food, careful boiling of equipment used, and increased emphasis upon the production of clean milk have all helped to reduce the incidence of "food poisoning" and its associated diarrheal states. It must be remembered that the average food poisoning is due to bacterial contamination (staphylococci or salmonella) and not specifically ptomaines.

Casparis prefers to classify those diarrheas generally called noninfectious as being due to irritations. Overfeeding, improper feeding, chilling, teething, and similar conditions probably impair the digestive capacity of the individual concerned. More careful supervision and adjustment of the food intake will prevent many diarrheas from developing when conditions are not favorable to the complete digestion and assimilation of the normal diet. Gastrointestinal allergy represents a condition about which we are rapidly learning to avoid the development of unpleasant gastrointestinal reactions by judicious and intelligent handling of the diet. List of conditions often associated with diarrhea:

1. Guanidine (toxin) with rapid dehydration as in superficial burns. Administration of calcium is helpful (physiologic antagonist).
2. Nutritional edema with low serum protein.
3. Vitamin C deficiency. A good nutritional background is important factor in recovery.

These conditions probably influence blood vessel permeability.

DR. KEITER.—Until the past two years treatment has been based on the concept that this disease is self-limited; that if one maintains the water balance, restores blood corpuscles and serum protein by transfusions, and waits, the vast majority of infants will recover. It is true that most of them will, but the duration of the infection and symptoms may vary from two to three weeks, to eight, ten,

or twelve weeks, under such treatment. Periods of starvation, allowing the gastrointestinal tract rest from the necessity of digestion and absorption of food, have been regarded as favorably influencing the course of the disease. Often after the period of starvation when food is offered, the diarrhea becomes worse, and two, three, and even four periods of starvation are resorted to until athrepsia occurs. Often there is no choice in this course of action since digestion and assimilation are at such a low ebb that nutrition is impossible. It is not likely that many physicians still regard bismuth as exerting any influence on the course of infection or paregoric doing more than to promote intestinal stasis, distention, and possibly cause some slight decrease in tenesmus.

Starvation is an essential part of the treatment. These infants cannot digest and assimilate food. The giving of formula only promotes a tremendous outpouring of gastrointestinal secretions, fermentation and distention, and adds volume to the fluid lost in the stools. We starve these infants until the fever subsides, the abdominal distention disappears, and the stools are reduced in frequency to two or three in twenty-four hours. Ordinarily the stools then have a yellow or brown color even though the baby is on a starvation regime, which color itself indicates the slower peristaltic activity of the bowel. After this occurs we start the infants on acid evaporated milk (equal parts of 1 per cent acid diluent and evaporated milk without added carbohydrate).

Adequate fluid intake and starvation will allow most infants to overcome the less severe infection in two or three weeks. It is unusual for one to recover sooner. More severe infections, however, may persist for several weeks or be rapidly fatal in spite of these measures, transfusions, correction of chemical imbalance, control of convulsions, and the numerous other measures ordinarily resorted to. What has been needed for many years is a specific remedy for the infection. Sulfanilamide seems to be practically that.

Since the use of sulfanilamide the duration of the infection following the regime just outlined has decreased to one week or less in the vast majority of cases. During the past summer none of our cases has lasted longer than two weeks and practically all the infants have been well and taking acid evaporated milk in one week. Reports on the failure of sulfanilamide to control this disease, we believe, are due to the fact that food was not withheld and that fluids were not adequately given. Sulfanilamide alone will not cure the disease. But, with the other factors controlled, we are convinced that sulfanilamide is the deciding factor. We give enough to produce and maintain a slight cyanosis, observing the white blood cells daily or every other day. We continue the administration of sulfanilamide for some three to six days after the stools have become normal and the patient again taking the formula.

The necessity for maintenance of the water balance is essential. Not only must the patient remain hydrated, but diuresis is desirable. Diuresis relieves toxemia but diuresis cannot occur in the presence of diarrhea unless the fluid intake is tremendously large. This problem has been solved.

In 1937 we reported how infants with dysentery will take tremendous volumes of fluid by mouth if given in the form of sweetened Ringer's solution. Subsequent years have proved this to be true without exception. For example, we recently treated an infant 4 months old who ingested 4 L. of Ringer's solution daily for several days in succession, all the while maintaining excellent hydration and producing a tremendous diuresis. We resort to parenteral fluids only when the infant is extremely weak, unconscious, or has such severe stomatitis that he cannot suck the nipple. When patients are first brought in for treatment, occasionally they are so severely dehydrated and nauseated that one or two injections of subcutaneous fluid by mouth seldom need to be repeated. Not only has the oral

administration of sweetened Ringer's solution largely obviated the necessity for parenteral administration of fluid to these infants, but it has also made it unnecessary to hospitalize the vast majority of them.

Ringer's solution contains calcium chloride, 0.25 Gm., potassium chloride, 0.3 Gm., and sodium chloride, 0.7 Gm., to the liter of solution. Our druggists dispense it in 25 times this concentration. The mothers prepare it by adding two and one-half tablespoonfuls and one tablespoonful of ordinary table sugar to a quart of boiled water. Older infants may not take this willingly from the start and in such instances we add some orange juice or Coca-Cola to the first few bottles. We have never seen any harmful effects from either. It is amazing how universally children approve of the taste of Coca-Cola and many times older infants who have been weaned from the bottle will drink Ringer's solution quite well from a Coca-Cola bottle, especially if the first few bottles have been flavored with it.

We continue giving Ringer's solution generously between feedings for a week or two after feedings have begun. As a rule, the fluid intake drops sharply as the diarrhea stops and the formula is increased. Usually the formula is started in feedings of 3 or 4 ounces every four hours and increased 1 ounce to each feeding daily until the infant gets all he will take.

In very severe cases of long duration when there has been essential starvation for days or weeks before we get the patient, we find nutritional edema a common occurrence. This yields quickly to transfusion while transfusion usually is indicated at the same time for an accompanying anemia. Before the use of sulfanilamide we occasionally saw transfusion act almost specifically on the course of the infection. The fever would drop promptly and the stools improve. This was attributed to antibodies thought present in the blood. But this effect was not regular or frequent enough to be expected in any given case. However, the beneficial effects of sulfanilamide are now confidently expected in all these cases.

Most of these infants show evidence of vitamin deficiency. Most of them are suffering from this deficiency even before they become infected, since their environment is so poor. Cod-liver oil concentrate and crystalline vitamins B and C are injected intramuscularly. Stomatitis and glossitis, which occur frequently in these babies, yield promptly to this treatment.

An extreme degree of anorexia is sometimes encountered as a late manifestation of the disease. The vitamin B preparations intramuscularly quickly relieve this. We have not resorted to gavaged feedings in these infants since we have learned the efficacy of vitamin B parenterally.

A frequent complication is excoriation and ulceration of the buttocks. This is treated by cleansing the skin with oil and applying an ointment of 3 per cent xeroform in Lassar's paste (without salicylic acid).

Prolapse of the rectum is not unusual in severe cases. This is treated by strapping the nates together with adhesive. It should go all the way around the hips, leaving an opening over the anus.

Severe acidosis when encountered is treated with molecular sodium lactate, orally and parenterally.

Convulsions are treated by chloroform inhalations for their immediate control and by sodium amytal or phenobarbital for long-continued effect. Phenobarbital seems to be a safe effective drug for combating the restlessness and excitement sometimes encountered in these patients.

Since the advent of sulfanilamide it has been unnecessary to feed protein milk, diluted skimmed milk, apple powder, agar-agar, or any of the other numerous feedings sometimes employed. There is no place for such feedings in our present concept of proper treatment.

Summary.—To summarize this concept of therapy, we repeat that now we have a specific therapeutic agent if used in conjunction with adequate fluid administration,

starvation, and vitamin restoration. Measures which cause intestinal stasis are counter to nature's efforts for proper drainage of the bowel. Therefore we give no opiates. We feed none of the special foods used in diarrhea because they do not really nourish the patient and simply are so much foreign matter for ejection in the stools. At the same time they promote the excessive secretion of digestive juices, giving greater volume to the stools and increasing their dehydrating tendency. Blood transfusion is used as indicated for anemia or serum protein deficiency.

Successful outpatient management of these cases naturally has done much to lighten the economic burden on a class of people least able to bear the high cost of hospitalization.

DR. WINTERS.—The pectin-agar preparation was developed in an attempt to overcome the disadvantages of the raw fruit diets and at the same time to retain the good points and to eliminate the necessity of starvation which has always been a basic principle in all types of diarrheal therapy. Influenced by the experimental and clinical work of Malyoth, Bauman, and others showing that pectin and cellulose were the active agents in the apple therapy, a combination of pectin and agar-agar plus dextrimaltose was devised. Although the proportions have been changed several times, the product as used the last three years was essentially 6.3 per cent pectin, 4.3 per cent agar-agar, and 89.4 per cent dextrimaltose. These are mixed together in a powder, which is used in the milk for the feedings of the infant or child suffering the diarrheal symptoms.

Method.—Two basic forms of feedings have been found very practical. A fluid form which is used for the nurslings or for gavage purposes is made in the proportion of 1 cup of the pectin-agar sugar to 24 ounces of milk, while for the older child, who is spoon-fed, the more concentrated combination of 1 cup of powder to 16 ounces of milk is used. The milk is added slowly to the powder and the combination cooked in a double boiler ten to fifteen minutes with occasional stirring. The more fluid form is placed in nursing bottles in the quantity desired for each feeding. When cold, this forms a soft gel which upon reheating and shaking will break down into a smooth thick liquid and can be fed through a nipple with an enlarged opening. The infants take the feedings as readily as do the older children. However, we have found that it is sometimes necessary to add flavoring such as chocolate, vanilla, or peppermint, or sliced bananas, banana powder, or various colorings to overcome the objections which were sometimes encountered with the older children. However, during the last three years one-half skimmed and even whole milk have been used with equal success.

No starvation period was used and no other food was given by mouth except glucose water which was offered ad libitum. To combat the dehydration which was present in some degree in practically every case, fluids were given intravenously and in some cases subcutaneously; and, when more normal circulatory volume had been re-established, one or two, and in the severe cases even four or more, small blood transfusions were given.

When it was felt that the improvement in the child's condition warranted a return to the normal formula, the amount of pectin-agar powder was progressively reduced for a few days with the subsequent resumption of the standard feeding routine. The older children were given a transitional diet consisting of two or three feedings of the pectin-agar gel with a modified soft diet fairly high in protein and containing only the bland fruits and very little vegetable material. After a few days the pectin-agar feedings were discontinued and the regular diet resumed.

Results.—Of 52 cases of specific dysentery and 27 cases of infectious gastroenteritis, which were probably dysentery, soft stools appeared on the average of from seven to thirty-four hours after the pectin-agar feedings were first given,

with an abrupt reduction in the average total number of evacuations daily. In the milder cases the response was often rather spectacular with soft stools appearing within a few hours after the first pectin-agar therapy; but in the more severe and toxic cases, while the appearance of the first soft stools was fairly prompt (twenty-four to seventy-two hours), the general improvement was often slow although steady.

The average intake per pound ranged from 33 to 52.4 calories and weight gains resulted in each group. The periods of straight treatment averaged from 6.5 to 12.9 days and the transitional diet was given from 4 to 14.8 days. The mortality ranged from 0 in gastroenteritis groups of 1936 and 1938 to the high of 53.3 per cent in the bacillary dysentery group of 1937. The mortality for the entire series was 26.6 per cent. The median age of all the patients reported was 10 months.

The stools resulting from this therapy have a peculiar soft consistency. We wish to emphasize that with this type of diet a great deal of indigestible bulk should be given to make four or more large and bulky stools daily. This is why it seems better in interpreting the response to this therapy to be guided more by consistency, whether it is soft or liquid, and the stool content, whether pus, blood, or mucus is present, rather than by the number or volume of the stools. The prompt appearance of soft stools and the decrease in number of liquid evacuations are of utmost importance in checking the excessive loss of fluids from the already dehydrated infant. In the dysentery cases the stools gave the characteristic foul odor with varying amounts of blood, pus, and mucus. In some stools blood occurred in small streaks, and in others practically nothing but blood and mucus was present. In the stools of the patients fed pectin-agar, the disappearance of the blood, pus, and mucus was measurably more prompt than in the stools of comparable patients treated with other diets, including protein milk, acid milk, and raw apple.

The rationale of giving a high carbohydrate milk feeding may be questioned by some as it was by us. We have found that the carbohydrate tolerance for our mixture is surprisingly high, and, when it is incorporated in the milk to supply the protein, our patients, in spite of the severity of the disease, have not only maintained their weights but also have shown weight gains. In our original study no milk was used; however, experience has taught us that high concentrations are equally well tolerated, even in severe specific dysenteries. Special feedings devised for a few extremely marasmic infants, incorporating powdered milk, egg yolk, and vitamin concentrates to give caloric values as high as 100 calories per pound, have been used successfully and apparently have saved the lives of some who were getting progressively worse on other diets.

The addition of the pectin-agar powder to the fresh milk brings about a precipitation of the milk in an extremely fine-grained curd which probably tends to increase the digestibility of the milk.

The response to this type of feeding is measurably more prompt and complete than that observed in similar cases treated by other dietary means. The results from feeding the apple diet to a group of infants and children suffering from various types of diarrhea were compared with the results from a similar group given the pectin-agar feedings. It was found that when the raw apple was fed, longer periods of treatment and transition were required; recurrences were more frequent; the appearance of soft stools, the cessation of liquid evacuations and the disappearance of blood, pus, and mucus were not as prompt as in the group fed pectin-agar; the feedings were not as well taken, and there was a weight loss, as compared with a gain in weight observed in the pectin-agar group. Again in a comparison of the results from the use of lactic acid milk and pectin-agar in treatment of cases of bacillary dysentery, it was found that patients responded more

quickly to the pectin-agar feedings and required a shorter period of treatment, that 41 per cent liquid stools occurred with the lactic acid milk as compared with 28 per cent with the pectin-agar, and that liquid stools persisted in the lactic acid group for 16.2 days as compared with 8.9 days in the pectin-agar group.

The action of the pectin was felt to be, in part at least, a mucus-sparing or a protein-sparing action, probably due to the uronic acid content of the pectin, which acted in a manner similar to that of glucuronic acid.

The total action of this pectin-agar combination is not completely understood, but it would seem to be a combination of the physicochemical and mechanical actions of the materials. Since the agar and pectin make a gel which passes through the gastrointestinal tract as such, liquid stools, in most instances, are a physical impossibility. The formation of the gelatinous mass and the breakdown of the pectin with the liberation of galacturonic acid, the absorbing, emulsifying, detoxifying, and diverse other actions of pectin and its split products result in a cooperative action to give the total therapeutic effect.

Pectin-agar therapy is particularly suitable for treatment of these severe infectious diarrheas since it not only has a therapeutic action on the diarrheal symptoms, but also offers a well-balanced, nourishing, and easily digested food which tends to keep up the infant's resistance until the time when the natural immunity can be developed. This diet has proved very practical and workable in that its method of preparation is simple; the average child takes the feedings quite readily; and it is made from the stable standard powder which is not subject to seasonal supply.

To summarize: Fifty-two cases of bacillary dysentery and 27 cases of infectious gastroenteritis, probably dysentery, in infants and children treated with the pectin-agar dextrimaltose combination is reported.

There was a definite and quick response with soft stools within an average of thirty-four hours and a gradual and steady improvement in 73.4 per cent of the cases.

The caloric intake averaged from 33 to 52.4 calories per pound per day, and average weight gains were observed in every group.

The mode of action of this therapy is probably both physicochemical and mechanical, with the uronic acids playing an important part.

The diet is peculiarly suitable for infectious cases, since besides having a definite therapeutic action, it is high in calories, well balanced, and easily assimilated, and it maintains nutrition while the body has a chance to develop the necessary immunity. It is easily prepared, very readily taken, available, standardized, and safe. Our experience continues to confirm our early observations that this pectin-agar diet very definitely more quickly and completely produces formed stools with fewer recurrences than other accepted methods, including the apple diet.

DR. E. C. MITCHELL, Memphis.—Thirty-two cases developed diarrhea (dysentery) from a carrier who showed no clinical findings but who had lived in a tropical climate before migrating here. I have had good success using sodium thiocyanate according to Dr. Ivy's technique. Dosage of ½ gr. per kilogram given the first twelve hours, intravenously, for prophylaxis; in severe cases, 20 mg. per kilogram.

DR. T. G. FOLSOM, Huntington, W. Va.—Dr. G. M. Lyon has been using sulfanylguanidine as developed by Dr. Marshal of Johns Hopkins with good results. There were 20 cases of acute dysentery and 20 controls, dosage being 0.1 Gm. per kilogram for the first dose and subsequent doses were 0.05 Gm. every four hours for 72 to 96 hours or until the stools were five or less daily. There was some toxicity but the drug was more effective than other forms of sulfonamides and should be used early during the course of the disease.

CHAIRMAN QUILLIAN.—Dr. Merlin L. Cooper, of Cincinnati, has had a very rich experience in stool culture work. He and his associates prefer sodium desoxycholate citrate medium for detection of *Shigella paradysenteriae* since this medium inhibits the growth of Gram-positive organisms and of *Escherichia coli*. He lists the efficiency of various media commonly used in the following order: Sodium desoxycholate, citrate, McConkey's; eosin methylene blue, Endo's.

He also suggests that lactose cultures be observed for three to six weeks for differential identification of the Sonne type of *Shigella paradysenteriae*.

From all of our comprehensive discussions, we conclude: (1) that the physician must study his individual case along with conservative management; (2) that the trend has gone away from starvation to that of newer methods of feeding; (3) that there is an increase in amoebic and protozoa infections as a result of the increase in air travel; and (4) that diarrheas that have occurred as epidemics in the newborn have stressed the necessity of better handling and early therapy.

Academy News

New York.—One of the special activities to which some of the Academy members have interested themselves is the Mother's Milk Bureau aligned with the Children's Welfare Federation. A new processing and canning of breast milk has been operative and has supplanted the former freezing of the breast milk. With the National Committee, which has been set up within the Academy, standards are to be set for the guidance of all the milk bureaus in this country and Canada, if and when these standards have been adopted.

Another activity which has been of great interest to many is the problem of rheumatic heart disease. With a state plan now submitted to the Children's Bureau, funds have been made available by this Bureau for the long term care (Sanatorial) of children with rheumatic heart disease. Already, ninety-six beds have been made available at the Reconstruction Hospital in Haverstraw, N. Y., for such care; that is, for children who are still in the active phase of their infection. Most of the children will be taken from the acute hospital and will be treated on a somewhat similar basis as a child with tuberculosis. This hospital will become a training center for physicians and nurses interested in this disease.

One of our members, Dr. Harold W. Dargeon, at the Memorial Hospital is most interested in the setting up of a Central Registry for Tumors in Children. This might well come within the scope of the Academy, and such a registry would be more than a statistical bureau, important as that would be. Such a registry would predicate the important educational aspects which would be inherent in its proper functioning and would necessitate a close cooperation with pathologists and roentgenologists. Also, a close cooperation between State and City Departments of Health would be essential.

An effort has been made to have one of our members appointed to the State Advisory Council on Nutrition, as it is felt that a pediatrist well qualified in the problems of nutrition would be of great assistance to the Council, which is an integral part of the National Defense Program.

New Jersey.—The program, in New Jersey, consists of an integration of interest and activities between the Academy members, the Child Health Committee of the Medical Society of New Jersey (which is composed of Academy members), and the Bureau of Maternal and Child Health in the State Department of Health. This Bureau is headed by Dr. Julius Levy, a competent pediatrician and executive. The three subdivisions of the program are:

1. Premature care provisions and procedure.

2. Baby Keep-Well Stations. Attending physician supervised by selected members of the Academy.

3. Postgraduate clinical instruction of Baby Keep-Well Station attending physicians by Academy members. Each physician is paid $15.00 for the time devoted to getting to the station, supervising and instructing the attending physicians, and returning to his office. It equals $5.00 to $7.50 per hour. Frequent conferences are held by the members to reach agreement in procedure and content of instruction. Political influence is nil and only those members of the Academy who have devoted sufficient time and interest to uphold the aims of improving medical services are continued though all members have been invited to participate. No discrimination against any member is made unless he, himself, establishes the basis through manifest lack of interest or attendance.

The state chairman has sent out a questionnaire to the members and the implication from the number of replies received regarding army and navy service is that few, if any, of the New Jersey Academy members are, as yet, in federal service, though at least one, Dr. Edward P. Essertier, of Hackensack, is Chairman of the County Medical Draft Board.

The members of the Academy now serving as consultants to the Bureau of Maternal and Child Health of the State Department of Health are:

Dr. Samuel Blaugrund, Trenton
Dr. Vincent Del Duca, Camden
Dr. George W. Esty, Westfield
Dr. Arthur Heyman, Newark
Dr. Robert E. Jennings, East Orange
Dr. Sandor Levinsohn, Paterson
Dr. W. Blair Stewart, Atlantic City

Each physician in this group is conducting a series of monthly conferences with some ten or fifteen physicians, each having charge of a New Jersey State Department of Health Baby Keep-Well Station. These conferences are designed to cover the practical aspects of infant care and growth and development of parent education. The aim is to stimulate greater interest and to improve the practice of these physicians regarding child care, thereby raising the standards in each of the stations.

At the meeting of Region IV of the American Academy of Pediatrics in San Francisco on May 1, 2, and 3, 1941, the members present voted that $500.00 from the treasury be used for the purchase of drugs to be sent to the British Pediatric Society for use in war relief. This sum represented a part of the balance from funds received from the sale of space to commercial exhibitors at previous annual meetings.

Through the cooperation of Lederle Laboratories this expenditure was made within a short time following the San Francisco meeting. The company's generosity and interest in the project made possible the sending of 200,000 5 gr. sulfanilamide tablets and 26,000 0.5 Gm. sulfathiazole tablets, quantities greatly in excess of those obtainable at the usual professional discount prices.

The sulfanilamide tablets were sent in two separate packages, one on each of two special ships designated by the British War Relief and the American Red Cross, following clearance through the United States State Department.

The sulfathiazole tablets were shipped on four bomber planes direct from Los Angeles to Canada, thence to England via Newfoundland. In a previous letter the president of the British Pediatric Society mentioned that supplies of these drugs would be most welcome in England due to some considerable difficulty in obtaining them, sulfathiazole particularly.

Copies of three letters from British pediatricians, Dr. W. G. Wyllie, Dr. Charles McNeil, and Dr. Arthur Maitland-Jones follow.

14th June, 1941

Dear Dr. Nixon:

Your letter and the most generous assistance which you and your colleagues are affording us are most sincerely appreciated. With the large demands made on stores, supplies of sulfanilamide and sulfathiazole make your gift most timely and helpful. I am arranging with the Secretary of the British Paediatric Association for the suitable distribution of the drugs.

Your letter, which I see is dated 22nd May, reached me some days ago, but too soon for the parcels to have arrived, which have to be cleared through the customs. I therefore in this letter convey our gratitude for your promised gift of:

200,000 5 gr. sulfanilamide tablets.

26,000 ½ gm. sulfathiazole tablets.

I was particularly impressed to hear that part of the tablets were arriving in bomber planes across the Atlantic, and personally feel that that should double their efficacy.

Here in Great Ormond Street we have not received further damage in recent raids on London, although fortunate to have been so nearly missed in the last "Blitz."

With most sincere thanks to you and your colleagues,

I am,

Yours sincerely,
(signed) W. G. Wyllie, M.D., F.R.C.P.
Representative (London)
British Paediatric Association.

— —:

This generous act on the part of your members has followed a similar gift made by the Southwestern Paediatric Society, which has already been distributed.

Dr. Maitland-Jones, our secretary, will already have acknowledged and thanked you for this most generous gift. As President of our Association, I feel impelled to add on behalf of all our members, our deep appreciation, not only of the generous gift which will be of great service to our children, but also of the generous and sympathetic thoughts that inspired it. You may be sure that this action of your Society not only strengthens the links between American and British medicine, but also deepens the unity and sympathy of our peoples in the dangers and distress of the times.

I am,

Yours sincerely
(signed) Charles McNeil
President
British Paediatric Association.

— —:

As Secretary of the British Paediatric Association I write you offering our most cordial thanks for your very great generosity which is appreciated by everyone.

You may be interested to hear that I have arranged that the Ministry of Health should undertake the distribution of these drugs and every Children's Hospital in Great Britain will receive a certain proportion of them.

I also write to thank you not only for the drugs themselves, but for the interest and sympathy which lies behind the action of sending these drugs.

Yours sincerely,
(signed) Arthur Maitland-Jones
A. G. Maitland-Jones
Honorary Secretary, British Paediatric Association.

News and Notes

Dr. Samuel Z. Levine, Professor of Pediatrics at Cornell University, will deliver the tenth annual series of the Benjamin Knox Rachford Lectureship in Cincinnati on October 23 and October 24, 1941. The subject of the lectures will be "Physiologic Handicaps of Prematurity: Their Pathogenesis and Clinical Applications." They will be held as usual in the auditorium of the Children's Hospital Clinic and Research Building.

Dr. Israel J. Wolf, of Paterson, was awarded the Medical Society of New Jersey prize of $100.00 for the best paper submitted on a scientific subject during the year. The subject of Dr. Wolf's paper was "Treatment of Rickets with a Single Massive Dose of Vitamin B."

Dr. Ruth H. Weaver, Registrar of Vital Statistics in Pennsylvania, recently received the degree of Master of Public Health from the University of Pennsylvania.

On July 7 at the Hospital de la Miséricorde in Montreal, the Hon. M. Henri Groulx, Minister of Health in the Province of Quebec, formally opened the fourth annual "Cours de perfectionnement en pédiatrie," which is held each year under the direction of Dr. Paul Letondal, professeur agrégé de pédiatrie a la Faculté de médecine de l'université de Montreal.

This course is of particular interest because it offers to French-speaking physicians of the Province of Quebec an opportunity to obtain graduate instruction in pediatrics under the auspices of the leading French Canadian pediatricians, and at a very nominal fee.